STUDIES IN THE HOFMANN REACTION ON GLYCIDIC AMIDES

THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY
TO
THE ALIGARH MUSLIM UNIVERSITY
ALIGARH

1965. N. HAJELA

The work described in the thesis was done under the supervision of Dr. N.A.Abraham

A C K N O W L E D G E M E N T

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The infra-red spectra were recorded in this laboratory and at Ben May Laboratory for Cancer research, University of Chicago. The microanalyses were carried out at Laboratoire de Chimie, Ecole Normale Superieur, Paris through the courtesy of Dr. M. Vilkas and at Chemistry Research Laboratory of Australian Micro Analytical Service, University of Melbourne.The N.M.R. spectra were recorded at Ben May Laboratory for Cancer research, University of Chicago.

STUDIES IN THE HOFMANN REACTION ON GLYCIDIC AMIDES

ABSTRACT

THESIS SUBMITTED FOR THE DEGREE OF
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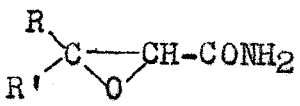
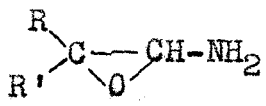
Hofmann Reaction of Glycidamides

A survey of the literature has shown that Hofmann reaction of glycidamides has not been studied. In the present work, Hofmann reaction on substituted glycidamides has been studied.

It was expected that glycidamide (I) when subjected to Hofmann reaction should yield the corresponding glycidamine (II) or the hydroxy aldehyde (III) (R and R' being hydrogen or alkyl or aryl groups). However, it was observed



(I)



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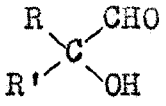
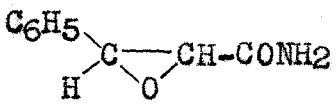


(III)

that glycidamines, the normal reaction product of Hofmann reaction or the hydroxy aldehydes into which the glycidamines may decompose, were not obtained in any of the examples studied. Hofmann reaction of 3-phenylglycidamide (IV) under special conditions using bromine and sodium methoxide in methanol, did not give the expected urethane (V).



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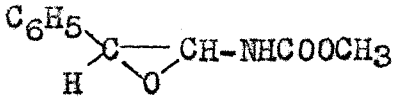


(V)

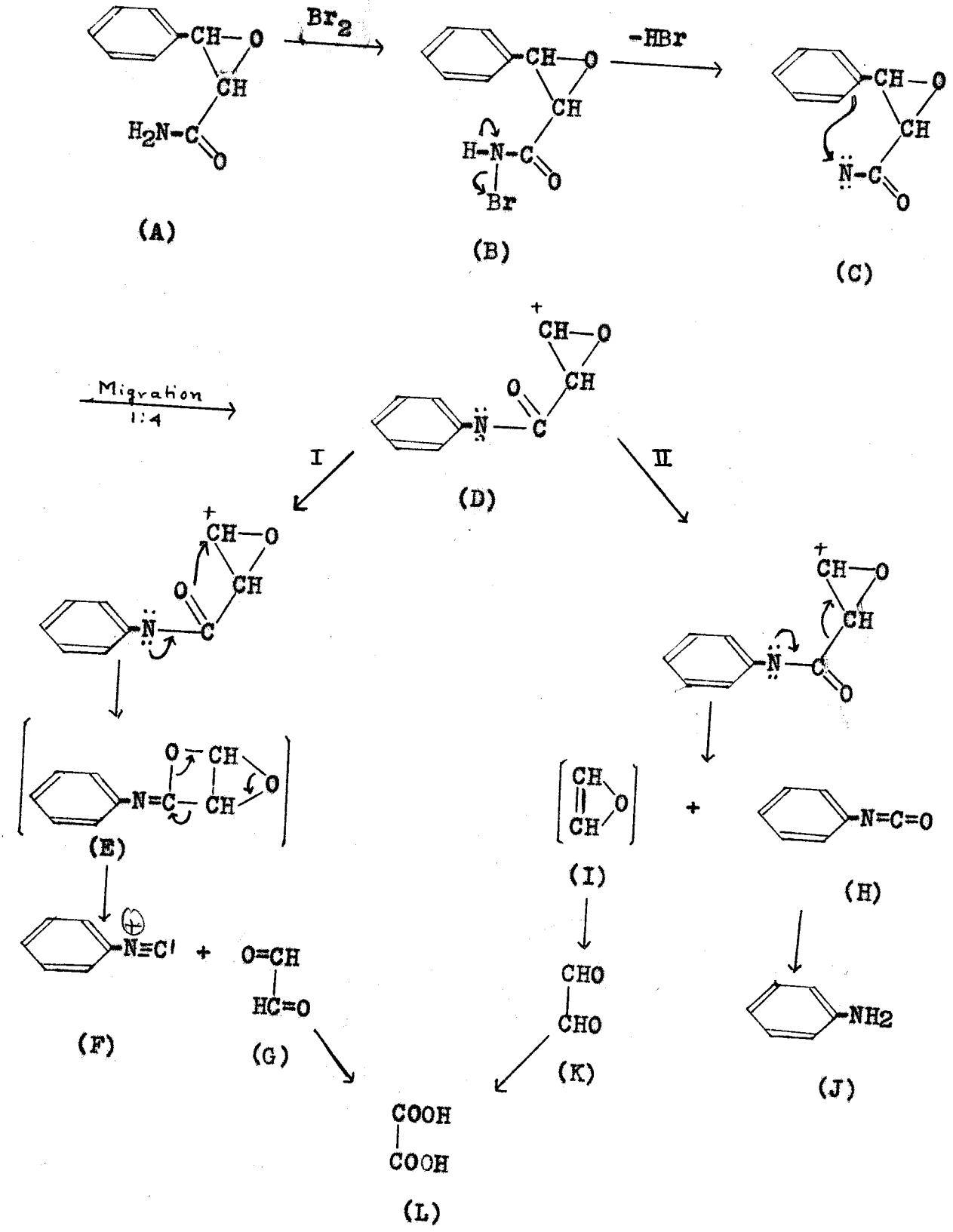
The following table summarises the compounds isolated and characterised in the Hofmann reaction of glycidamides. Sodium hypobromite was used as the reagent.

Table

S. No.	Amide	Products
1.	3-Phenylglycidamide	(a) Benzaldehyde (b) Aniline (c) Phenylisocyanide (d) Benzoic acid (e) erythro β-Phenylglyceric-acid
2.	3-(o-Chlorophenyl)-glycidamide	(a) o-Chlorobenzaldehyde (b) o-Chloroaniline (c) o-Chlorophenylisocyanide (d) o-Chlorobenzoic acid (e) erythro β-(o-chloro-phenyl)glyceric acid
3.	3-(m-Chlorophenyl)-glycidamide	(a) m-Chlorobenzaldehyde (b) m-Chloroaniline (c) m-Chlorophenylisocyanide (d) erythro β-(m-chloro-phenyl)glyceric acid
4.	3-(p-chlorophenyl)-glycidamide	(a) p-Chlorobenzaldehyde (b) p-Chloroaniline (c) p-Chlorophenylisocyanide (d) p-Chlorobenzoic acid (e) erythro β-(p-chloro-phenyl)glyceric acid
5.	3-(p-Toluyl)glycidamide	(a) p-Tolualdehyde (b) p-Toludine (c) p-Toluylisocyanide (d) p-Toluic acid (e) erythro β-(p-Toluyl)-glyceric acid

S. No.	Amide	Products
6.	3-(m-Nitrophenyl)-glycidamide	(a) m-Nitroaniline
7.	3-(p-Methoxyphenyl)-glycidamide	(a) Anisaldehyde (b) Anisic acid
8.	2-Methyl-3-phenyl-glycidamide	(a) Benzaldehyde (b) Benzoic acid (c) Phenylisocyanide (d) Aniline
9.	2-Methyl-3-(p-chloro-phenyl)glycidamide	(a) p-Chlorobenzaldehyde (b) p-Chlorobenzoic acid (c) p-Chloroaniline
10.	2,3-Diphenylglycidamide	(a) Benzaldehyde (b) Benzoic acid
11.	3,3-Diphenylglycidamide	(a) Benzophenone (b) An unidentified compound m.p. 240-50°
12.	3-Methyl-3-phenyl-glycidamide	(a) Acetophenone (b) Unreacted amide
13.	3,3-Pentamethylene-glycidamide	cyclohexanone

The reaction products obtained in the Hofmann reaction of glycidamides show that the reaction of alkaline sodium hypobromite on glycidamides proceeds along three paths simultaneously i.e. (a) oxidation resulting in the formation of aldehydes or ketones and carboxylic acids (b) hydrolysis resulting in the formation of glyceric acids and (c) an abnormal Hofmann reaction resulting in the formation of isocyanides

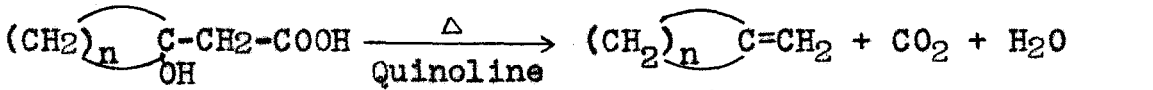

Br2
-HBr
(A)
(B)
(C)
Migration
1:4
I
II
(D)
(E)
(F)
(G)
(H)
(I)
(J)
(K)
(L)

C O N T E N T S

INTRODUCTION

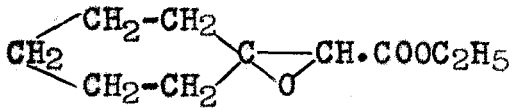
I N T R O D U C T I O N

The dehydrative decarboxylation of β-hydroxy acids and their t-butyl esters has been described in the literature[1,2]. β-Hydroxy acids and their t-butyl esters undergo dehydrative decarboxylation when heated with quinoline in the presence of pinch of copper powder. The products obtained are exocyclic unsaturated hydrocarbons of the type I. Such dehydrative decarboxylation takes place only when the β-hydroxy group is tertiary.



(I)

The present work was started with the hope of studying a similar type of decarboxylation on β-aminoacids where the amino group rests on a tertiary carbon atom. For the preparation of amino acids with the amino group on t-carbon atom, attempt was made to open the epoxide ring of the Ethyl 3,3-pentamethyleneglycidate (II)



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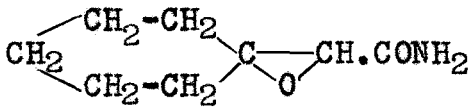


(III)

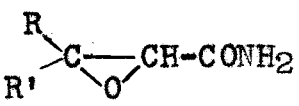
with ammonia. It was observed that opening of the epoxide

ring requires rather drastic conditions (heating in a sealed tube to a high temperature for many hours[3]). On the contrary the amide (III) of the glycidic acid was obtained easily and in good yield.

The obtention of large quantity of glycidamide prompted us to divert from the original project i.e. study of decarboxylation of β -aminoacids to the Hofmann reaction of glycidamides.

A survey of the literature has shown that Hofmann reaction on glycidamides has not been studied. In the work described in this thesis Hofmann reaction on different glycidamides has been studied.

It was expected that glycidamides (IV) when subjected to Hofmann reaction should yield the corresponding glycidamines (V) or the hydroxy aldehydes (VI). However it



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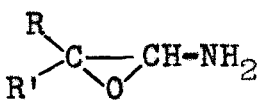

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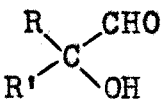


(VI)

was observed that the expected amine or aldehyde were not formed in the reaction, instead a mixture of isocyanide, aldehyde and amine was obtained along with hydrolysis products. The yields of these products were however, poor.

The formation of isocyanides by Hofmann

reaction represents an entirely new aspect of the reaction as isocyanides have so far been not reported as products of Hofmann reaction on amides of any type. A tenative mechanism is proposed for this abnormal Hofmann reaction.

The literature on Hofmann reaction has been reviewed by Wallis & Lane[4] upto 1942. Along with the representative examples of the Hofmann reaction from the literature already reviewed, a review of the literature from 1942 to 1964 has been included in this thesis. A table in the end summarises examples of Hofmann reaction from 1942 to 1964.

A brief review of various methods employed for the preparation of glycidic esters & glycidamides has also been included in the thesis.

HOFMANN REACTION

The Nature of the Reaction

The conversion of an amide into an amine with one carbon atom less by treatment with bromine or chlorine and alkali is known as Hofmann reaction.

$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2 + Br_2 + 4OH^- \longrightarrow R\text{-}NH_2 + CO_3^{=} + 2Br^- + 2H_2O$$

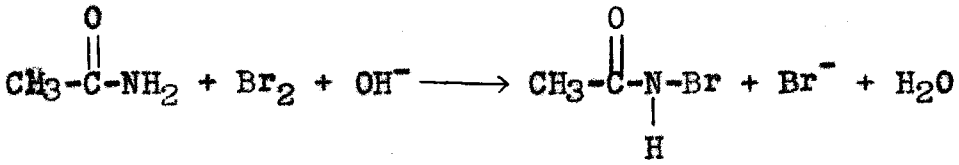
The Hofmann reaction is generally carried out by dissolving the amide in a very slight excess of cold aqueous hypohalite solution, followed by rapid warming and steam distillation if the amine produced is volatile. A valuable modification consists in carrying out the reaction in an alcoholic (usually methanolic) solution with subsequent hydrolysis of the urethane so obtained[4].

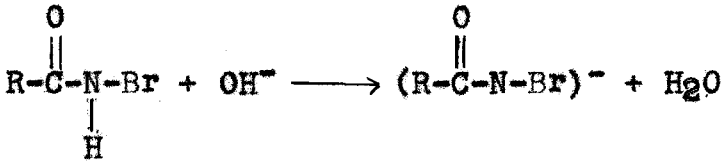
$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2 + Br_2 + 2OH^- + R'OH \longrightarrow R\text{-}NH\text{-}COOR' + 2Br^- + 2H_2O$$

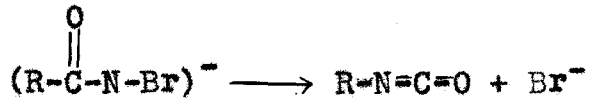
$$R\text{-}NH\text{-}COOR' + H_2O \longrightarrow R\text{-}NH_2 + CO_2 + R'OH$$

Hofmann observed that the reaction of acetamide with equimolecular quantities of bromine and alkali yielded N-bromoacetamide which reacts with alkali to give a unstable salt. In the dry state it undergoes decomposition wherein the organic residue migrates from the carbon to nitrogen

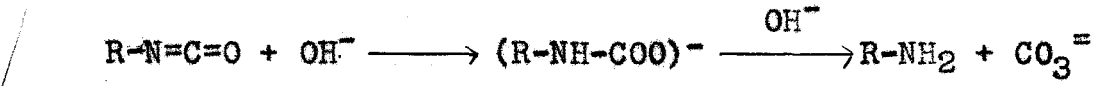
atom, the product being isocyanate and alkali metal halide[4].





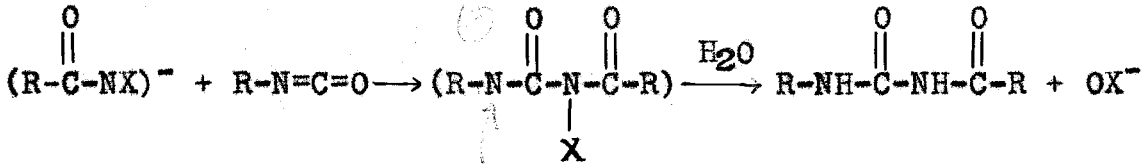


In the presence of water and excess of alkali, the isocyanate is hydrolysed to amine. In alcoholic solution it is converted



to urethane.

When one half of the usual quantities of bromine and alkali are employed, alkyl acyl ureas are obtained. The isocyanates in the absence of excess of alkali, react with the sodium salt of the haloamides to give salts of alkyl



acyl ureas from which ureas themselves result on hydrolysis.

Apart from the normal Hofmann reaction in which amines are formed, there are examples where the products of the reaction of hypohalite and amides are not amines. These include Hofmann reaction of amides of α,β -unsaturated acids, α -haloamides, α -ketoamides, α -nitroamides, α -hydroxy amides and aryl substituted semicarbazides and ureas.

The Scope of the Reaction

Aliphatic, Alicyclic and Arylaliphatic Amides

(a) Monoamides

Good yields of the corresponding monoamines are obtained from aliphatic monoamides unless the latter contains more than eight carbon atoms. Alkyl acyl urea formation predominates in these cases. Although amines arise from the hydrolysis of alkyl acyl ureaas, they are largely oxidised to nitriles by the excess of hypobromite present. With such amides, a modification of the usual procedure using methanol and sodium methoxide gives satisfactory results. Lauramide on treatment with aqueous alkaline hypobromite gives largely N-undecyl-N'-laurylurea[4], but treatment of the amide in methanol with sodium methoxide and bromine gives a 90% yield of methyl undecylcarbamate which may be converted with negligible loss to the desired amine.

Magnien and Baltzly[5] have attributed low yields of amines from fatty acids amides to the various side reaction. As the molecular weight increases, the isocyanate (the proximate rearrangement product), the product amine and the earlier intermediates have an increasing tendency to extract each other from solution, whereby the isocyanate is increasingly likely to react with other substances than hydroxide ion. By using

prepared sodium hypobromite and dioxane as inert cosolvent (to minimise side reactions), they have been successful in obtaining good yields of amines from fatty acid amides. However, above caramide the yield of amine did gradually diminish and palmitamide gave no amine at all.

(b) Alicyclic Monoamides

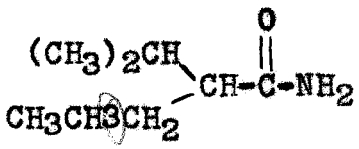
The isomeric o-, m- and p-hexahydrotoluamides have been converted through the urethanes into the corresponding aminomethylcyclohexanes in 70% yields[4].

(c) Arylaliphatic Monoamides

No special difficulties are encountered with arylaliphatic amides unless the aromatic ring contains hydroxyl or derived function in which event low yields may result from side reactions involving halogenation of the ring. β-(p-Methoxyphenyl)-propionamide gives on treatment with aqueous alkaline hypobromite only 35% of the desired amine[4] while p-hydroxybenzamide yields exclusively 2,6-dibromo-4-aminophenol[4]. The use of sodium hypochlorite which leads to a more rapid rearrangement improves the yield of amines in the Hofmann reaction of many amides containing phenolic or aromatic ether functions.

Unlike normal aliphatic amides, dialkyl acetamides give the corresponding symmetrical disubstituted ureas as byproducts when treated with 1 mole of bromine and

alkali, while reaction of 0.5 mole of bromine and alkali give a mixture of unchanged amide and disubstituted urea. Thus, on treating α-propyl-α-isopropylacetamide (VII) with 1 mole potassium hypobromite, 1-isopropylbutylamine (VIII) and 1,3-bis-(1-isopropylbutyl)urea (IX) is obtained. Reaction with 0.5 mole potassium hypobromite yields VII and IX only[6].



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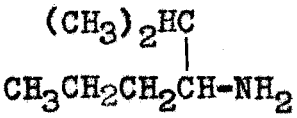

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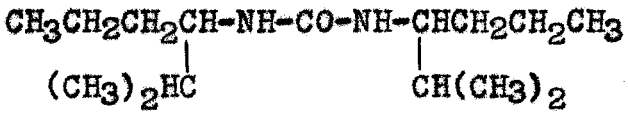
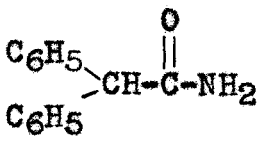


(IX)

Hofmann reaction with diphenylacetamide (X) and β,β-diphenylpropionamide (XI) has shown that while no difficulty was encountered with the latter, the former could be converted to the corresponding amine (XII) only in a more concentrated alkali solution (8 mole KOH per mole of amide) than is normally employed[7].



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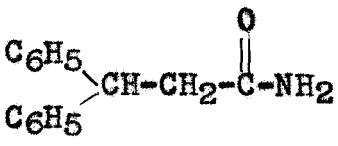

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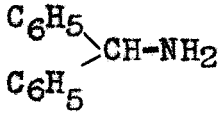
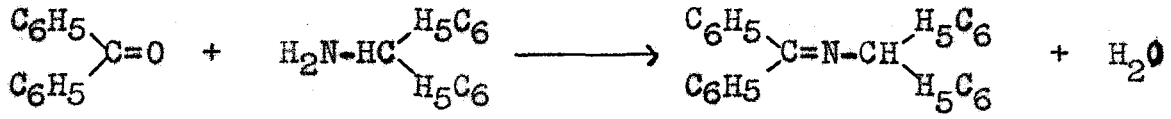


(XII)

During the experiments carried out to ascertain the optimum conditions for the successful Hofman reaction of diphenylacetamide, Rahman and Farooq[7] got a new secondary reaction product, a schiffs base; N-benzhydryl-benzophenone-imine (XIII) under slightly modified conditions*. The schiffs base is formed by condensation of benzophenone and benzhydrylamine which are produced during the reaction. The rearrangement has to be presumed to have taken place in cold resulting in the production of benzhydrylamine while benzophenone might have been formed by oxidation of some of the intermediates of the Hofmann reaction. Schiffs bases



(XIII)

were not obtained from phenylacetamide and β,β-diphenylpropionamide[8].

The Hofmann reaction of 4-strylphenylacetamide (XIV) yields 4-cyanostilbene (XV) and stilbene-4-carboxyamide

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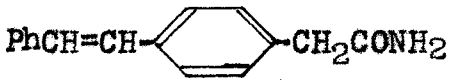
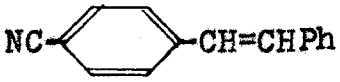
* 2.1 g (0.01 mole) amide was added with stirring to KOBr prepared from 2.5 g (0.04 mole) KOH in 80 cc water at 0°C. Stirring was continued for 10 hours. The reaction mixture was not heated.

(XVI)[9], the latter being the principal product. The production of nitriles by oxidation of amines, initially formed in the Hofmann reaction, has been reported earlier[10] notably in acetylinic derivatives but production of next lower homologue of the amide appears to be novel.



(XIV)



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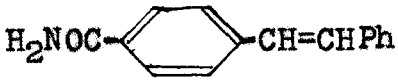
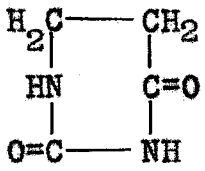


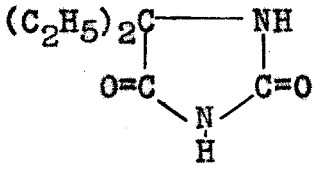
(XVI)

(d) Diamides

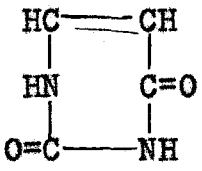
Diamides of adipic acid and its higher homologues are converted to diamines by aqueous alkaline hypobromite[4]. Hofmann reaction of succinamide gives dihydrouracil (XVII). At a higher temperature and with excess of alkali β-alanine is produced. The action of aqueous alkaline sodium hypochlorite on diethyl malonamide and maleinamide gives in analogous fashion C,C-diethylhydantoin (XVIII) and uracil (XIX) respectively[4].



(XVII)



(XVIII)



(XIX)

Treib and Hauptman[11] prepared a number of ω-amino carboxylic acids by selective Hofmann reaction of amides of dicarboxylic acids. Sodium salt of succinic acid semiamide (XX)on reaction with sodium hypobromite followed by acidification and esterification gives β-alanine ethyl ester (XXI) in 66% yield. Oxidation of sodium salt of glutaric acid semiamide with bromine and alkaligives 62% dipyrrolidinone. Reaction of bromine and sodium methoxide

$H_2N-CO-(CH_2)_2COONa$ (XX)

$H_2N-CH_2CH_2COOC_2H_5$ (XXI)

with methanol as solvent on methyl ester of adipic acid semiamide (XXII), the urethane (XXIII) was obtained in 88% yield. Hydrolysis of the urethane gives the 5-aminovaleric acid (XXIV) in nearly 100% yield. By a similar procedure amino acids $H_2N-(CH_2)_nCOOH$ (where n = 5,6,7,8, & 12) were prepared.

$H_2N-CO-(CH_2)_4COOMe$ (XXII)

$MeOOC-HN-(CH_2)_4COOMe$ (XXIII)

$H_2N-(CH_2)_4COOH$ (XXIV)

(d) Monoacid monoamides

The action of dilute solution of barium hydroxide and barium hypobromite converts l-β-malamidic acid to l-isoserine[4]. Higher amidic acids like the higher monoamides are best treated with sodium methoxide and bromine in

methanol solution instead of aqueous hypobromite or hypochlorite.

Mono- or disubstituted malonamic acid upto those containing ten carbon atoms in the chain, give no byproducts other than amino acids when subjected to Hofmann reaction[12]. The Hofmann reaction of lower members of disubstituted malonamic esters give amino acid esters while the higher members give mixture of amino acid esters and symmetrical bis-(carbethoxyalkyl)ureas. The Hofmann reaction of lower members of monosubstituted malonamic esters (isopropyl and isoamyl) give the amino acids instead of esters, while the same reaction on higher members (octyl) give only the hydrolytic products (octyl malonamic acid).

A number of new amino acids have been synthesised from cyanoacetic esters by converting the cyanoacetic esters into malonamic esters by treatment with suitable reagents followed by Hofmann reaction. These include α,α-diisopropyl-, α,α-dipropyl-, α,α-diisobutyl-, α,α-dibutyl-, α-isopropyl-α-propyl-, α-isobutyl-α-butyl-, α-ethyl-α-propyl-, α,α-diisoamyl-α-aminoacetic acids, α-amino-α-isopropylvaleric acid and α-amino-α-isopropyl-caproic acid[13].

The alicyclic amidic acids are converted easily to amino acids with aqueous alkaline hypochlorite. The

isomeric truxillamidic acid and truxinamidic acids give the corresponding truxillamic and truxinamic acids without any difficulty[4].

(f) Ethylenic amides

α,β -Unsaturated amides give satisfatory yields of urethane when treated with methanolic sodium hypochlorite. Thus, cinnamic amide gives 70% yield of methyl strylcarbamate[4]. Hydrolysis of these urethanes leads directly to aldehydes. However, β,γ - and γ,δ -unsaturated amides

$$C_6H_5\text{-}CH{=}CH\text{-}CONH_2 \xrightarrow[CH_3OH]{NaOCl} C_6H_5\text{-}CH{=}CH\text{-}NH\text{-}COOCH_3$$

$$\xrightarrow{HOH} C_6H_5CH_2CHO$$

give the corresponding amines in poor yields[4].

(g) Acetylenic amides

Nitriles are obtained from the Hofmann reaction of α,β -acetylenic amides[4].

$$R\text{-}C{\equiv}C\text{-}CONH_2 \longrightarrow (R\text{-}C{\equiv}C\text{-}NH_2) \longrightarrow R\text{-}CH_2\text{-}C{\equiv}N$$

N-Chloro-2-octynamide, for example, on treatment with barium hydroxide gives enanthonitrile in 70% yield[4].

(h) α -Ketoamides

Hofmann reaction has been studied only on Benzoylformamide. Instead of the expected amide, benzoic acid or methyl benzoate are the only products isolated in the reaction [4,14].

(i) α -Nitroamides

Only one compound of this type has been subjected to Hofmann reaction. Ratz[15] reported earlier that when nitroacetamide is reacted with an aqueous solution of sodium hypobromite, a mixture of di- and tribromonitromethane is obtained. Brownstein[15] on reinvestigation found that the product is dibromonitromethane.

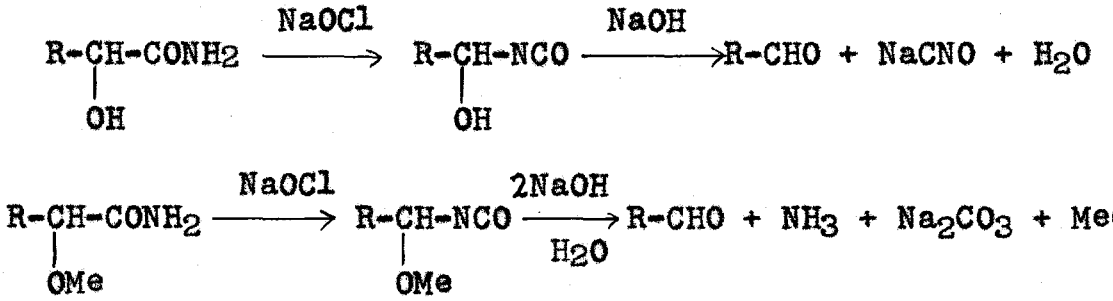
$$O_2N\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2 \longrightarrow O_2N\text{-}CH\text{-}Br_2$$

(j) α -Hydroxyamides

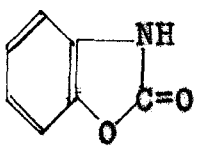
Hofmann reaction of amides of α -hydroxy acids result in the formation of aldehydes. Thus, d-gluconamide gives d-arabinose and benzaldehyde is obtained from mandelamide[4]

$$R\text{-}\underset{\underset{OH}{|}}{CH}\text{-}CONH_2 \longrightarrow \left[R\text{-}\underset{\underset{OH}{|}}{CH}\text{-}NH_2\right] \longrightarrow R\text{-}CHO + NH_3$$

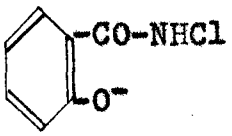
Ault & coworkers[16] have established that hydroxy amides and aqueous alkaline hypobromite yield aldehyde and cyanate while methoxy amides yield aldehyde and ammnnia but no cyanate. Their findings have been confirmed by Haworth & coworkers[17].



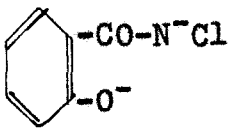
Salicylamide with hypochlorite in strongly alkaline solution yields 4;5-benzoxazol-2-one (XXV) but in less basic solutions 5- and 3-chloro-2-hydroxybenzamides are formed[18].



(XXV)



(XXVI)

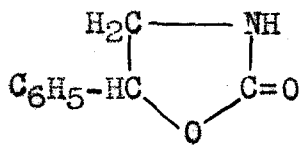


(XXVII)

Arcus and Greenwood[18] conclude that the anion (XXVII) of N-chloroamide is formed only when the hydroxyl ion concentration is high, electron release from the existing phenoxide ion (XXVI) opposing the removal of second proton. The Hofmann reaction is, therefore, inhibited in solutions

which are not strogly alkaline and substitution by hypochlorous acid, hypochlorite ion or chloramine then occurs in the nucleus.

Reaction of β -hydroxy-β-phenylpropionamide with bromine and methanolic sodium methoxide yields 5-phenyloxazolid-2-one (XXVIII)[18].



(XXVIII)

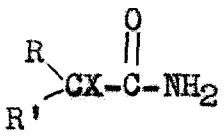
(k) α -Haloamides

Gryskiewicz-Trochimwski & co-workers[19] observed that Hofmann reaction of trifluoroacetamide yields hexafluoroethane. But this has since then, shown to be incorrect by Barr & Haszeldine[20] who reported that the actual product is bromotrifluoromethane and not hexafluoroethane.

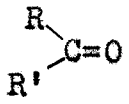
Ascher[21] reported formation of trichloromethylamine as the normal reaction product of trichloroacetamide and potassium hypobromite but this product could not be isolated by later workers. Hine & Rosscup[22] found it to be trichlorobromomethane.

Stevens & Coffield[23] observed that Hofmann reaction of α -haloamides (XXIX) yield corresponding dialkyl

ketones (XXX) generally in 40% to 70% yields. Thus,



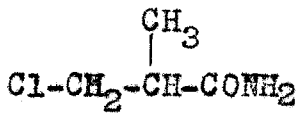
(XXIX)



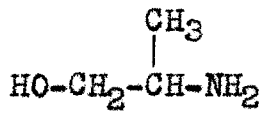
(XXX)

(X = halogen)

2-bromo-2-methylbutyramide gives 53% ethyl methyl ketone and 2-bromo-2-ethylhexanamide gives 70% normal butyl ethyl ketone. However, β-haloamides failed to give aldehydes or ketones. With β-chloro-isobutyramide (XXXI) a 49% yield of 2-amino-1-propanol (XXXII) was obtained.



(XXXI)

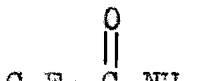


(XXXII)

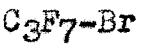
Rodionov, Alekseeva and Vaver[24] also reported formation of aldehydes from Hofmann reaction of α-haloamides. Thus, 2-bromo-3-methylbutyramide and 2-chlorohexanamide when subjected to Hofmann reaction give isobutyraldehyde and valeraldehyde respectively in good yields.

They also showed that best yields of aldehydes are obtained by treatment of α-bromoamide with alkaline hypochlorite with immediate removal of aldehydes from the reaction mixture. The yields of aldehydes were not improved by substituting the bromo derivative for the chloro derivative.

Husted & Kohlhase[25] observed that gemdihalides are obtained in the Hofmann reaction of amides of aliphatic perfluoroacids and that the reaction proceeds through N-bromoamides. Thus, heptafluorobutyramide (XXXIII) on reaction with sodium hypobromite gives 65-70% perfluoropropylbromide (XXXIV). Reaction of sodium hydroxide on N-bromoperfluorobutyramide and N-bromoperfluoroacetamide give bromoperfluoropropane and bromotrifluoromethane respectively.



(XXXIII)



(XXXIV)

Gem dihalides as the main reaction products of Hofmann reaction of α-haloamides are also reported by Stevens, Mukherji & Traynelis[26]. They have shown that the conditions of the Hofmann reaction can be varied to increase either the yield of the ketone or of the gemdihalide. α-Hydroxyacids were also obtained from the residual solutions. Thus, α-bromoisobutyramide when subjected to Hofmann reaction by one procedure (reaction mixture was allowed to remain at 0°-5° for 66 hours followed by heating to 50°C and then working up according to usual procedure) gives 54% gemdihalide (2,2-dibromopropane), 10% acetone and 31%

∝-hydroxyisobutyric acid. While another procedure (reaction mixture stirred for ten minutes, heated rapidly and steam distilled) gives only 10% 2,2-dibromopropane and 68% acetone.

Barr & Haszeldine[20] in reinvestigation of Hofmann reaction of perfluoroamides came to the conclusion that Hofmann reaction with perfluoroamides can show duality of mechanism to give high yields of either R_fX (X = Cl or Br) or R_fNCO. The bromo compound, for example, is formed by elimination of the isocyanate ion from R_fCON^-Br in a solvent of high dielectric constant, whereas pyrolysis of the anhydrous salt $(R_fCONBr)^-Na^+$ gives R_fNCO with intermediate formation of $R_fC\ddot{O}\ddot{N}:$.

Patterson, Wilson & Trimnell[27] also studied Hofmann reaction of perhaloamides. They observed that trichloroacetamide with sodium hypobromite gives variable yields of bromotrichloromethane (34-53%), cyanate (73-80%) and ammonia and chloroform in small amounts. However, decomposition of N-bromotrichloroacetamide with sodium hydroxide solution gives reproducible yields of bromotrichloromethane (56%), cyanate (88) and ammonia and chloroform in small amounts. Reaction of N-bromotribromoacetamide with aqueous sodium hydroxide gives carbontetrabromide (39%), cyanate (74%) ammonia and bromoform.

Aromatic and Heterocyclic amides

(a) Aromatic amides

In the absence of free or alkylated phenolic hydroxyl groups, Hofmann reaction of aromatic amides like benzamide and naphthamide, proceeds normally and corresponding amines are obtained in good yields. However, if free or alkylated hydroxyl groups are present in the aromatic amides, halogenation of the ring is likely to occur with serious lowering of the yield of the amine. This effect is minimised by the use of hypochlorite and large excess of alkali[4].

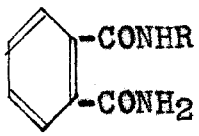
(b) Phthalamides and Phthalimides

Hofmann reaction of phthalimides and substituted phthalimides result in the formation of anthranilic and substituted anthranilic acids. In the latter case, usually one of the two possible isomer predominates. The predominance of one isomer can be explained on the basis of known electronic and vicinal effects[4].

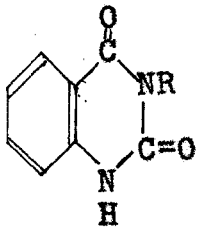
Putokhin[28] isolated dimethylcarboxyanthranilate and little dimethylcarboxycarbanilylphthalamate by reaction of sodium methoxide in methanol on bromophthalimide. It has been suggested that the reaction proceeds through the stage of R-C(OBr)(OH)NH2. This reaction mechanism is also suggested for the Hofmann reaction in general, avoiding the customary details[28,29].

Successful application of the reaction has also been made to the half amides of aromatic dicarboxylic acids. For example, 2-carboxy-4,5-dichlorobenzamide is converted readily by the action of alkaline sodium hypochlorite to 4,5-dichloroanthranilic acid[4].

Intramolecular reaction to give substituted 2;4-dihydroxyquinazolines was not observed in the case of Hofmann reaction of 4-nitro-, 3-nitro- and 4-chloro-phthalamides. The products isolated were corresponding substituted anthranilic acids[30]. However, in contrast to this behaviour, treatment of N-methylphthalamide and N-ethylphthalamide (XXXV) with alkaline potassium hypochlorite give 3-methyl- and 3-ethyl-2;4-diketo-1;2;3;4-tetrahydroquinazolines (XXXVI) respectively[30].



(XXXV)



(XXXVI)

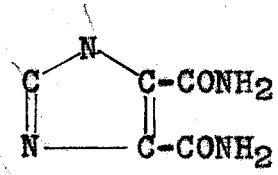
(R= CH_3 or C_2H_5)

(c) Heterocyclic amides

Hofmann reaction on various heterocyclic amides has also been studied. 1,2,2,5,5-Pentamethylpyrrolidine-3-carboxamide has been converted to 1,2,2,5,5-pentamethyl-3-aminopyrrolidine by alkaline potassium hypobromite[4].

Xanthines[31,32,33,34], copazolines[35], pyrimidines[35]

and alloxazines[36] have been obtained from heterocyclic diamides having two adjacent amido groups by intramolecular reaction. Thus, glyoxaline-4;5-dicarboxyamide (XXXVII) gives xanthine (XXXVIII) when subjected to Hofmann reaction[34].



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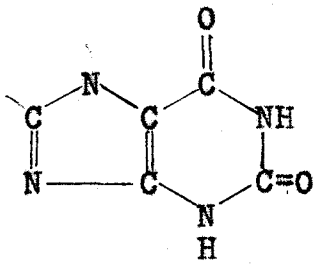
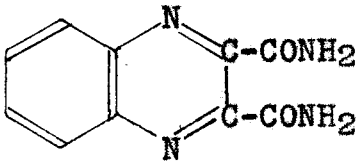
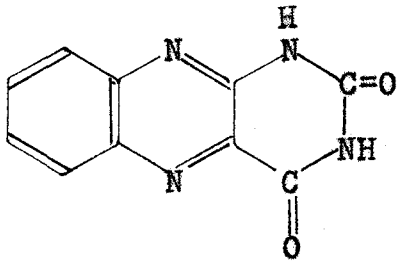


(XXXVIII)

Quinoxaline-2;3-dicarboxyamide (XXXIX) when reacted with 2 mole potassium hypobromite and excess of alkali, gives alloxazine (XL) while reaction with 1 mole of potassium hypobromite gives 2-aminoquinoxaline-3-carboxylic acid (XLI)[36].



(XXXIX)



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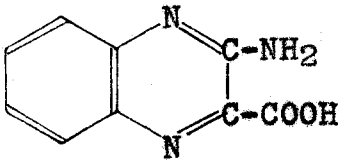
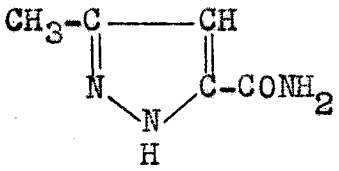


(XLI)

In the Hofmann reaction only 4-substituted pyrazolecarboxamide react normally to give the corresponding amines[37]. If fourth position is free, bromination takes place at this position and the amide group is not attacked. In some cases large excess of potassium hypobromite gives 4-bromoamines. Thus, 3-methyl-5-pyrazolecarboxamide (XLII) gives with potassium hypobromite, 3-methyl-4-bromo-5-pyrazolecarboxamide (XLIII) while excess of potassium hypobromite gives 3-methyl-4-bromo-5-aminopyrazole (XLIV).



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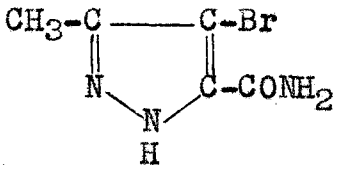

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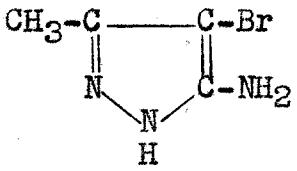
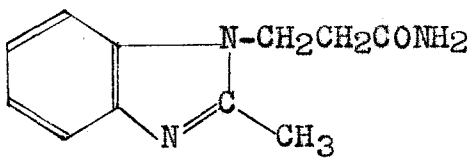
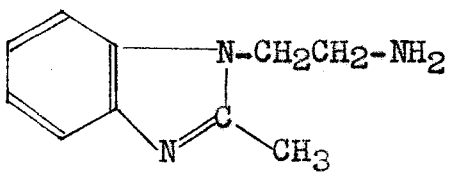


(XLIV)

Hofmann reaction of substituted β-(1-benzimidazole)propionamide give the corresponding substituted 1-(β-aminoethyl)benzimidazoles[38]. Thus, the reaction of sodium hypobromite on 2-methylbenzimidazolepropionamide (XLV) gives 1-(β-aminoethyl)-2-methylbenzimidazole (XLVI) in 59% yield.



(XLV)



(XLVI

Aryl Semicarbazides and Ureas

Aryl semicarbazides are first oxidised by hypochlorite to aryl diazocarboxamide ($Ar-N=N-CONH_2$) which apparantly undergo the usual rearrangement. The expected product ($Ar-N=N-NH_2$), however, being immediately oxidised by hypochlorite to an aryl azide. The overall reaction thus, consumes three molecules of hypochlorite.

$$Ar-NH-NH-\overset{\overset{O}{\|}}{C}-NH_2 + 3OCl^- + 2OH^- \longrightarrow ArN_3 + 3H_2O + CO_3^{=} + 3Cl^-$$

Phenyl semicarbazide may be converted to phenylazide in 30% yield[4].

A limited application of the reaction has been made to aryl ureas. N-Chloro-N'-2,4,6-trichlorophenylurea gives 2,4,6-trichlorophenylhydrazine on treatment with alkali. N-Chloro-N'-phenylurea, however, gives p-chlorophenylhydrazine as the only isolable product[4].

Poly Amides

With a view to improve the quality of the polymers, Hofmann reaction has been applied in recent years to polymers having amide groups. Hofmann reaction on the

following polymers has been described in the literaure:

Polymethacrylamides[39]

Polymeric amides[40]

Polyacrylamides[41,42]

Polyvinylamides[43]

Halogenated rubbers[44]

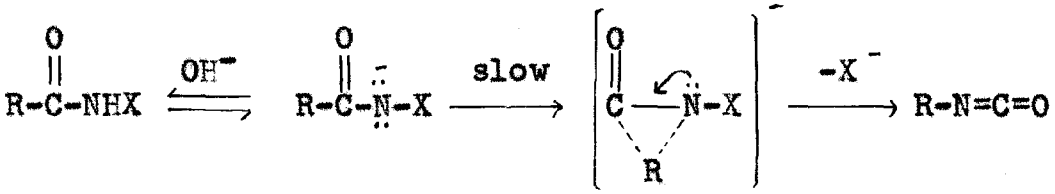
Poly-L-glutamine[45]

Poly-D-glutamine[46].

Mechanism of Normal Hofmann Reaction

Hofmann reaction proceeds through the conjugate base of the N-haloamide $(R.CO.NX)^-$ formed from the N-haloamide by abstraction of the proton by base, for salts containing anions of this type may be prepared and may be shown to rearrange rapidly to isocyanate. Moreover, halogenated N-alkylamides (R.CO.NR'X) which can not form such anions, do not undergo the rearrangement[47].

The Hofmann reaction may be represented as a rearrangement which involves a simple 1,2-shift. This may be represented as:



(XLVII)

$$R\text{-}N{=}C{=}O \xrightarrow{H_2O} R\text{-}NH_2 + CO_2$$

The loss of the halide ion from the anion (XLVII) gives the species $R.CO.\ddot{N}:$ in which the nitrogen atom has only a sextet of valency electrons. If this electron deficient nitrogen had any independent existence, such a molecule would react rapidly with water to give hydroxamic acid (R.CO.NHOH), whereas no hydroxamic acid or products closely

related to it have been found in the reaction mixtures[47]. The departure of the halide ion and the shift of the migrating group in the Hofmann reaction are simultaneous. This assumption has been confirmed by the observation that the configuration of the migrating group is retained in the reaction. Some examples are cited below.

(a) The action of bromine and alkali on (+) 2-methyl-3-phenylpropionamide gives optically pure (+) 2-~~methyl~~amino-3-phenylpropane[4]. The same optically pure amine may be obtained from (+) 2-methyl-3-phenylpropionazide by the Curtius rearrangement as well as from the derivatives of (+) 2-methyl-3-phenylhydroxamic acid by the Lossen reaction*.

---

* The Hofmann, Curtius and Lossen rearrangements as indicated by the following equations are quite similar:

$$(RCONX)^- \longrightarrow R\text{-}N{=}C{=}O + X^- \qquad \text{(Hofmann)}$$

$$(RCON_3) \longrightarrow R\text{-}N{=}C{=}O + N_2 \qquad \text{(Curtius)}$$

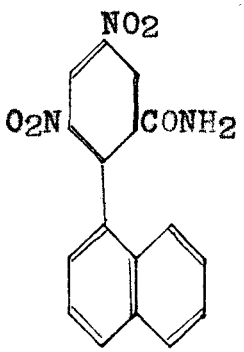
$$(RCONOCOR')^- \longrightarrow R\text{-}N{=}C{=}O + R'COO^- \qquad \text{(Lossen)}$$

Any of these reaction may be represented by the equation:

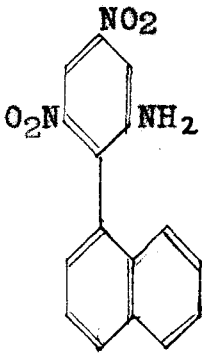
$$R\text{-}\overset{\overset{O}{\|}}{\underset{B}{C}}\text{-}NA \longrightarrow AB + R\text{-}\overset{\overset{O}{\|}}{C}\text{-}\ddot{N}: \longrightarrow R\text{-}N{=}C{=}O$$

(XLVIII)

(b) The Hofmann reaction of (+) 3,5-dinitro-2-α-naphthylbenzamide (XLIX) leads to optically pure (+) 3,5-dinitro-2-α-naphthylaniline (L)[4]. Here the optical



(XLIX)



(L)

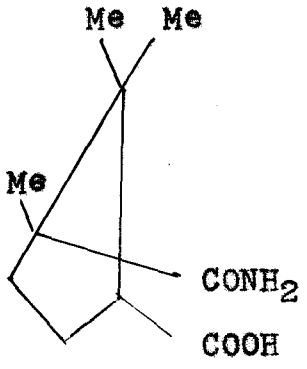
activity is due to restriction of rotation about the pivot bond between the benzene and naphthalene nuclei. If at any time during the migration, the migrating group had been free, the restriction would have been removed, and atleast partial racemisation would have occurred.

(c) Hofmann reaction of β , β ,β -triphenyl-propionamide gives only the expected amine i.e. β , β , β -triphenylethylamine. Here the migrating group, if free, is extremely susceptible to rearrangement[4].

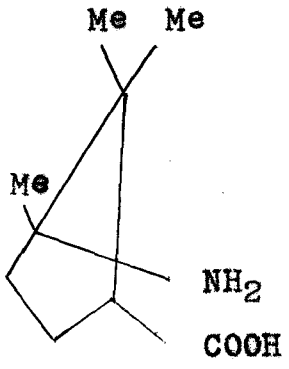
---

and the driving force of the rearrangement may be presumed to arise from the tendency of electron deficient nitrogen atom of the fragment (XLVIII), to acquire electrons from the neighbouring carbon atom. (AB = HX in Hofmann, N_2 in Curtius and KOCOR' in Lossen rearrangements respectively)

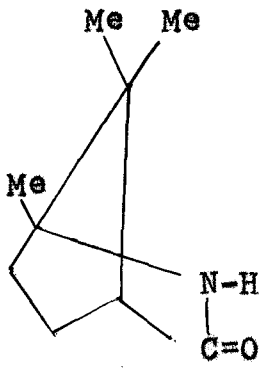
It has been established that in the rearrangement of this type the group R does not undergo Walden inversion. Thus, when the amide (LI) from camphoric acid in which the COOH and $-CONH_2$ groups are cis to each other, is subjected to Hofmann reaction, amino acid (LII) results. In the latter the -COOH and $-CONH_2$ groups also lie cis to each other, for this acid rapidly forms lactam (LIII). The trans amino acid (LIV) which would result from inversion of configuration at the migrating carbon should not form such a lactam .



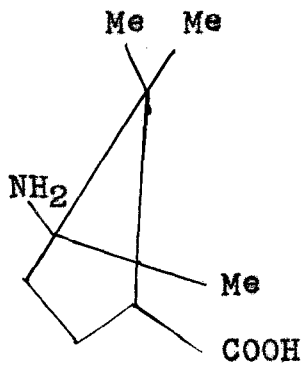
(LI)



(LII)

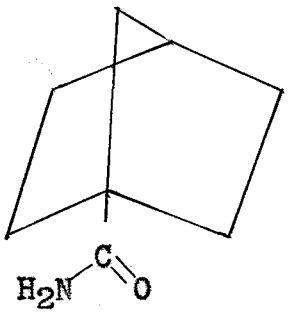


(LIII)

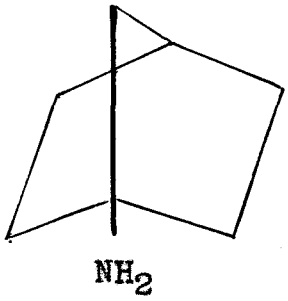


(LIV)

Moreover, the bicyclic amide (LV) readily undergoes the Hofmann reaction. In this case the rigidity of the ring system prohibits inversion of configuration at the α- carbon[47].



(LV)



(LVI)

Kenyon's work with optically active compounds has shown that Beckman, Hofmann, Curtius and Lossen rearrangements occur with retention both of asymmetry and molecular configuration[48].

Prosser & Eliel[49] have provided an altogether independent proof for the intramolecular nature of Hofmann reaction. Pointing out that certain carbanion intermediates have been shown to involve retention of optical and geometrical configurations and that carbanion reaction may proceed normally at bridgehead carbon atoms, they argue that the overwhelming stereo-chemical evidence for retention of configuration cannot be taken as very convincing proof for the intramolecular nature of the reaction.

Prosser & Eliel subjected the mixture of m-D-$C_6H_4CONH_2$ (benzamide m-d) and $C_6H_5CON^{15}H_2$ (benzamide $-N^{15}$) to Hofmann reaction, so that if the reaction is to any extent intermolecular, the product should contain some m-D-$C_6H_4N^{15}H_2$ (aniline-m-d-N^{15}). Mass spectroscopic investigation of this mixture after the reaction, showed it to be free of m-D-$C_6H_4N^{15}H_2$.

The rate determining step in the Hofmann reaction is the release of the halide ion from the haloamide anion as the rearrangement of N-bromobenzamides is accelerated by incorporation of electron donating groups ($-CH_3$ & $-OCH_3$) and retarded by electron withdrawing groups ($-NO_2$ & $-CN$).[47]

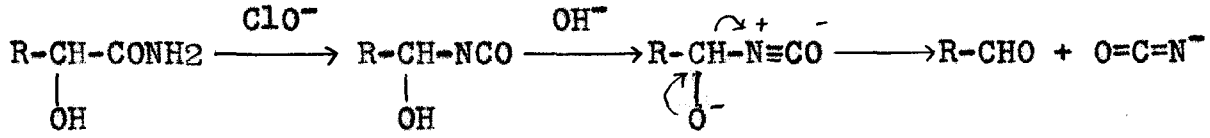
Recently Putokhin[29] proposed an altogether new mechanism for the Hofmann reaction. He suggested that during the halogenation of amides and imides, the halogen replaces a hydrogen atom attached not to nitrogen but of the OH group on carbon (of the tautomeric pseudoacid form R.C:NH (OH) of the amide). This halogen is positively charged and comparable to that in hypobromite. The halide subsequently undergoes the following changes to give the isocyanate. Hydrolysis of the isocyanate gives amine.

$$R\text{-}\overset{OBr}{\overset{|}{C}}\text{=}NH \longrightarrow R\text{-}\overset{+}{C}\text{=}NH \overset{\bar{O}Br}{\longrightarrow} R\text{-} + O\text{=}C\text{=}N\text{-} + HBr$$

$$R\text{-} + O\text{=}C\text{=}N\text{-} \longrightarrow R\text{-}NCO \xrightarrow{\text{Hydrolysis}} R\text{-}NH_2 + CO_2$$

Mechanism of Abnormal Hofmann Reaction

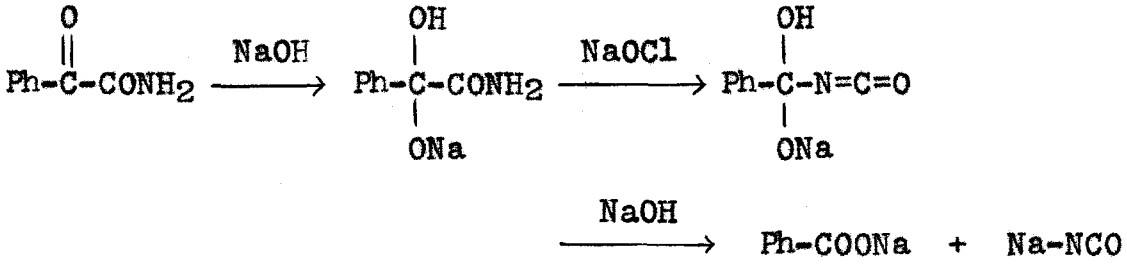
Arcus[14,18] proposed the following mechanism for the weerman degradation of ∝ -hydroxyamides in the Hofmann reaction to an aldehyde:



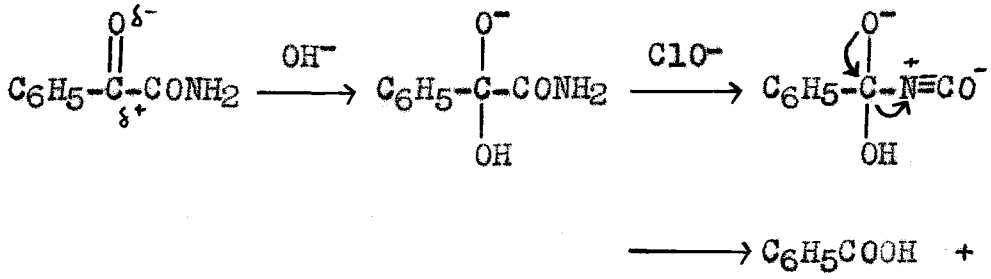
(LVII) (LVIII)

In the hydroxy isocyanate (LVII) the electron attracting isocyanate group renders the hydroxyl hydrogen weakly acidic and the anion (LVIII) is formed, electron displacements as shown then yield the aldehyde and the cyanate ion. The reaction as a whole being one of elimination. Methylation of the hydroxyl group renders this process impossible in accordance with experimental findings that methoxyamide yield aldehyde and ammonia but no cyanate (cf. p 16).

Rinkes[50] proposed the following mechanism for the formation of sodium benzoate and sodium cyanate from benzoyl formamide:



Arcus and Prydal's[14] work substantiate the above course of the reaction. It has been found that benzoyl isocyanate reacts vigorously with aqueous alkalies to give nearly pure benzamide and only a trace of cyanate ion. It is apparant that benzoyl isocyanate, the 'normal' product of the Hofmann reaction of benzoyl formamide, can not be formed during the reaction with aqueous alkaline hypochlorite. They conclude therefore, that the interaction of benzoyl formamide with hydroxyl ion precedes conversion of amide into isocyanate. They have proposed the following mechanism for the complete reaction, the electron movements being identical with those proposed for the Weerman reaction.

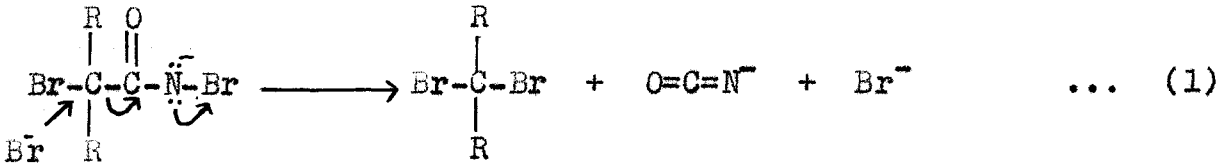


$$\longrightarrow C_6H_5COOH + O{=}C{=}N^-$$

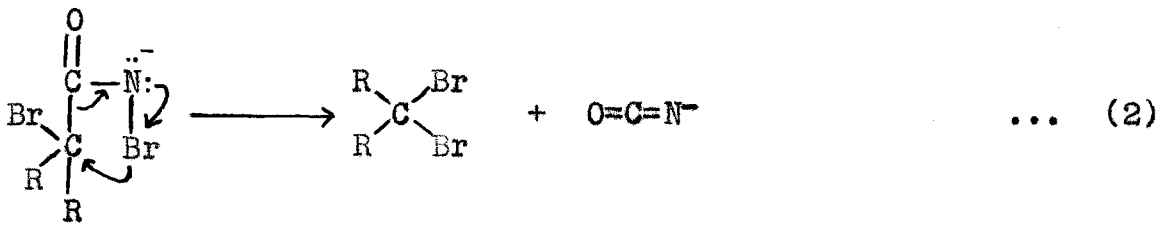
Stevens & co-workers[26] obtained gem dihalides and ketones from Hofmann reaction of α-haloamides of acetic, propionic, butyric, isobutyric, methyl acetic, and diethyl acetic acids. Cyanate ion formation was observed to accompany gem dihalide formation. They prepared a N-bromo-α-haloamide independently and subjected it to Hofmann reaction, the product was a gem dihalide. However, the corresponding

α-haloisocyanate was hydrolysed immediately by water containing bromine ions to give only the ketone, indicating that the N-bromoamide is an intermediate but α-haloisocyanate is not an intermediate in the production of gem dihalides. Husted & Kohlhase[25] working on aliphatic perfluoroamides also reached the same conclusion.

Stevens & co-workers[26] observed that the N-bromoamide in the presence of bromide ion and absence of base did not give the gem dihalide. One reasonable conclusion is that the N-bromoamide ion is the intermediate that gives the gem dihalides and the cyanate ions. Whether the reaction involves displacement by bromine ion as indicated by equation 1 or a cyclic mechanism as indicated by equation 2, is still not clear.



... (1)

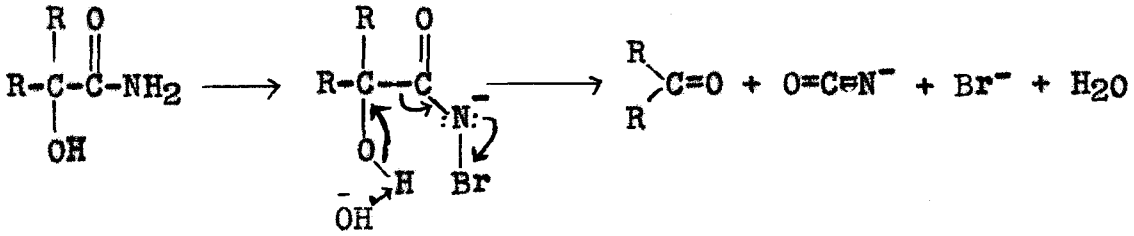


... (2)

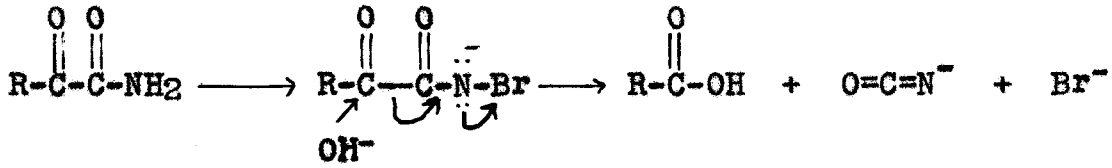
On the basis of these experiments Stevens & co-workers suggested the following alternate mechanism to

the one proposed by Arcus for the ∝-hydroxyamides[14] and for the ∝-ketoamides[14].

Mechanism for ∝-hydroxyamides:



Mechanism for ∝-ketoamides:



Brownstein [15] obtained dibromonitromethane by Hofmann reaction of ∝-nitroacetamide. He isolated an intermediate and found it to be N-∝-dibromonitroacetamide ($C_2H_2Br_2N_2O_3$). The reaction occurs in two steps:

$$O_2N\text{-}CH_2\text{-}CONH_2 + 2OBr^- \longrightarrow O_2N\text{-}CHBr\text{-}CONHBr + 2OH^- \quad \ldots (1)$$

$$O_2N\text{-}CHBr\text{-}CONHBr + H_2O \longrightarrow O_2N\text{-}CH\text{-}Br_2 + CO_2 + NH_3 \quad \ldots (2)$$

Barr & Haszeldine[20] observed that depending on experimental conditions, Hofmann reaction with perfluoroamides can show duality of mechanism to give High yields of either R_FX (X= Br or Cl) or R_FNCO (Cf. p.20)

The failure to obtain R_FNCO or its hydrolysis products C_2F_5CN, $C_2F_5CONH_2$ or $C_2F_5COONH_4$, show that Hofmann reaction with perfluorobutyramide ($C_3F_7CONH_2$) under normal condition does not occur. The failure to obtain a perfluoroamine, however, cannot be taken as evidence that the normal Hofmann reaction has failed because heptafluoro-n-propylisocyanate is known to be hydrolysed readily with water to give via the the nitrile and the amide, the ammonium salt of fluoroacid containing one carbon atom less in the perfluoroalkyl group[51]. Thus, even if the Hofmann reaction proceeds normally with a perfluoroalkylamide, the product in the alkaline medium prevailing, would be the sodium salt of the shorter chain acid.

$$C_3F_7NCO \xrightarrow{NaOH} C_2F_5COONa + 2F^- + CO_2 + NH_3$$

The failure to obtain the known decomposition products of the amine prove that the isocyanate is not produced as an intermediate.

Curtius rearrangement of perfluoroacylhalide proceedss normally and gives isocyanate in good yields[51]. It shows that the intermediate $RFCO\ddot{N}$: once formed can rearrange even when R_f is a strogly electronegative perfluoroalkyl group.

The Arndt-Eistert reaction also proceeds

normally with perfluoroacids[52]. Trifluorodiazoacetone, for example, decomposes smoothly in ethanolic solution to give ethyl β,β,β-trifluoropropionate. The mechanism clearly involves the rearrangement of an intermediate similar to $R_fCO\ddot{N}$:, to give the ketene which then reacts with ethanol to give the ester.

$$CF_3\text{-}CO\text{-}CHN_2 \longrightarrow N_2 + CF_3\text{-}CO\text{-}\ddot{C}H \longrightarrow CF_3\text{-}CH{=}C{=}O$$

$$CF_3\text{-}CH{=}C{=}O + C_2H_5OH \longrightarrow CF_3\text{-}CH_2COOC_2H_5$$

The success of Curtius and Arndt-Eistert reactions with perfluoro compounds clearly show that the failure to obtain an isocyanate or its subsequent hydrolytic products in the Hofmann reaction of perfluoroamides, is caused by failure of formation of $R_fCO\ddot{N}$: as intermediate under the conditions employed.

The salt $(C_3F_7CONBr)^-Na^+$ is quite stable in contrast to very unstable salts obtained from N-bromoalkylamides. The failure of $(R_fCONX)^-Na^+$ to lose X^- (X = Cl or Br) must thus be the reason for the change in mechanism of Hofmann Reaction.

$$(R_fCONBr)^- Na^+ \longrightarrow R_fBr + Na\text{-}N{=}C{=}O \qquad \text{(Abnormal)}$$

$$(RfCONBr)^- Na^+ \longrightarrow R_f\text{-}N{=}C{=}O + NaBr \qquad \text{(Normal)}$$

The failure of bromine to separate from R_fCON^-Br as bromide can be attributed to the strogly electronegative perfluoroalkyl group. The Curtius and Arndt-Eistert reactions by contrast involve loss of a neutral molecule (N_2) in the key stage. rather than the loss of an ion and such a process

$$RCON_3 \longrightarrow R\ddot{C}O\ddot{N}: + N_2 \qquad \text{(Curtius reaction)}$$

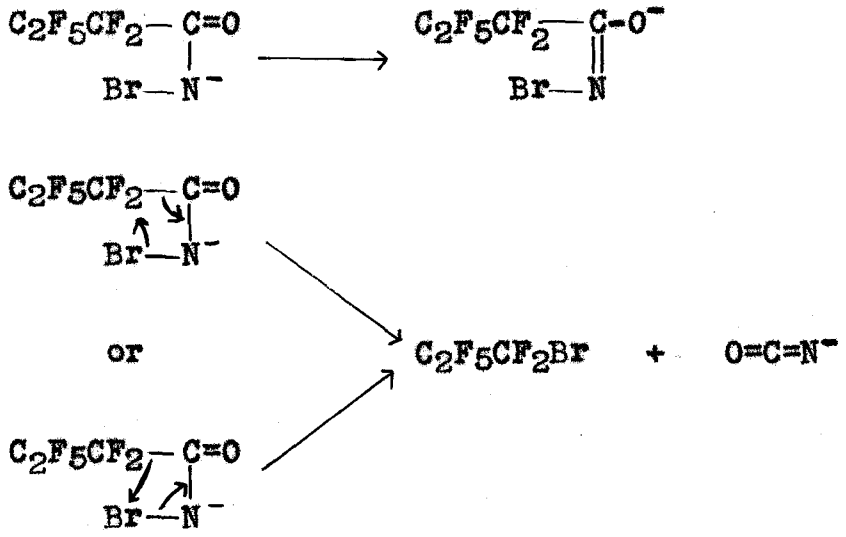
$$RCOCHN_2 \longrightarrow RCO\ddot{C}H + N_2 \qquad \text{(Arndt-Eistert reaction)}$$

will clearly be considered less sensitive to the electron attracting demands of the group R_f.

Barr & Haszeldine are of opinion that attack of bromide ion or bromine cation on α carbon atom of R_fCONBr^- is unlikely in view of high yields of R_fBr obtained by heating $(R_fCONBr)^-Na^+$ alone with water. A two stage process involving intermediate R_f ion is also unlikely since such carbanions are known to abstract hydrogen from solvent or lose fluoride to give olefine. Neither heptafluoropropane nor hexafluoropropene is found among the products. Husted & Kohlhase[25] reported the formation of heptafluoropropane from the reaction of sodium hypoiodite and heptafluoro-butyramide. It is, however, produced under conditions which cannot be regarded as normal for the Hofmann reaction.

The most probable mechanism as proposed by Barr and Haszeldine[20] involves intramolecular ejection of a

cyanate ion. They have proposed the following mechanism for the Hofmann reaction of perfluoroamides;



The 1;3 shift of R from carbon to bromine will be facilitated by the marked positive character of bromine and negative character of R_f group.

It is noteworthy that although chloro compound R_fCl can be prepared from the perfluoroamide, attempts to prepare the perfluroiodoalkane R_fI by the reaction of perfluoroamide with sodium hypoiodite failed and hydrolysis to the sodium salt of the acid predominates probably since the iodine has sufficient positive character for the 1;3 shift to occur in an ionising solvent.

$$C_3F_7CONHI \longrightarrow I^+ + C_3F_7CONH_2 \xrightarrow{OH^-} C_3F_7COONa$$

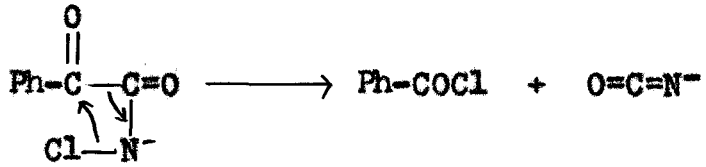
The elimination of cyanate ion as proposed by

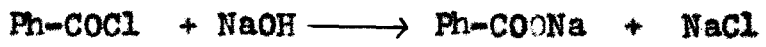
Barr and Haszeldine, from R_fCONX^- involves the free ion in a polar solvent such as water and the sodium ion plays no essential part in the reaction. Clearly, however, if the sodium ion is deliberately kept in proximity to the R_fCONX^- e.g. as in the crystal lattice of the anhydrous salt, then at a suitable temperature, reaction to yield NaX and intermediate $R_f\ddot{C}O\ddot{N}$ and thence R_fNCO (isocyanate) should not be impossible. This prediction was adequately confirmed by preparation of heptafluoropropylisocyanate in 83% yield when the anhydrous salt $(C_3F_7CONBr)^-\ Na^+$ was heated to 170°C.

$$C_3F_7\text{-}C(=O)\text{-}\ddot{N}\text{-}Br\ (Na^+) \longrightarrow NaBr + C_3F_7\text{-}C\ddot{O}\ddot{N}: \longrightarrow C_3F_7\text{-}NCO$$

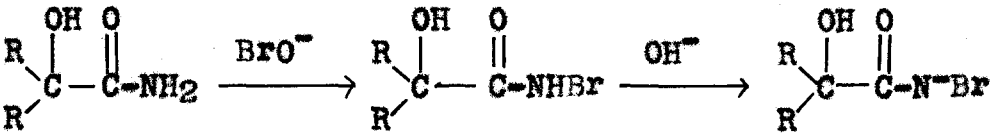
It is expected (because perfluoroalkyl group is extremely electronegative) that amides containing other electro negative groups will also show similar behaviour. It is likely that in Arcus's[14] mechanism for the Hofmann reaction of α-ketoamides, an intermediate such as $Ph.CO.CO.NX^-$ would lose halide in aqueous solutions only with difficulty and a scheme analogous to that proposed for perfluoroamides has been suggested by Barr & Haszeldine for the α-ketoamides and α-hydroxyamides.

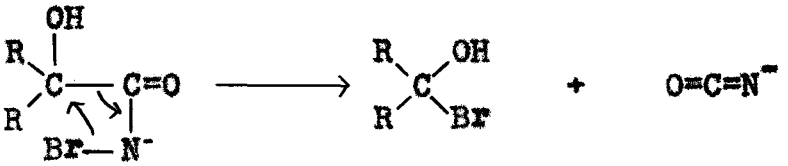
Mechanism for α-ketoamides:

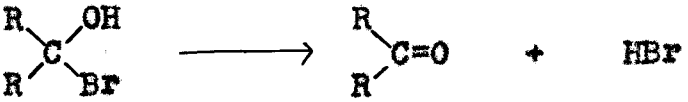




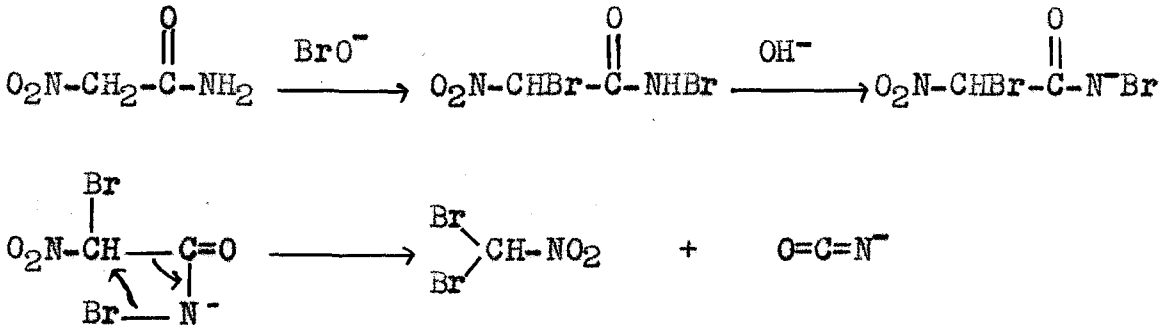
Mechanism for α-hydroxyamides:







The mechanism for the formation of dibromonitromethane by Hofmann reaction of α-nitroacetamide[15] may also be represented on the pattern proposed by Barr & Haszeldine for the α-haloamides, α-ketoamides and α-hydroxyamides.



Patterson & co-workers[27] consider that in the Hofmann reaction of trihaloacetamides, the reaction follows three paths simultaneously i.e. hydrolysis of the amide, a normal Hofmann reaction to give the trihalomethylamine and an abnormal Hofmann reaction resulting in the production of bromotrihalomethane.

N-Bromotrichloroacetamide may react with base to form the anion or undergo hydrolysis to give the amide which in turn may be converted into acid and ammonia. The ammonia produced may be regarded as evidence of this hydrolysis. Since only a maximum of 7% cyanate is hydrolysed to ammonia under the reaction conditions employed, the contribution from cyanate is not significant.

Patterson & co-workers are of opinion that the major products (bromotrichloromethane or carbon tetrabromide and cyanate) formed in the Hofmann reaction of trichloro- and tribromoacetamides arise when the anion of N-bromotrihaloacetamide $(CX_3CONBr)^-$ undergoes either a normal reaction to form the amine or an abnormal reaction

to form the halogen compound.

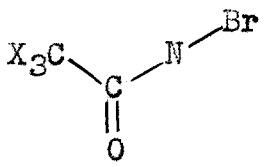
Barr & Haszeldine[51] observed that the perfluoroalkylamines are readily dehydrohalogenated to nitriles in media of high dielectric constant. By analogy trichloro- or tribromomethylamines produced by the normal Hofmann reaction, may be expected to undergo dehydrohalogenation to the corresponding nitrile (chloro or bromo cyanogen) which have been reported to decompose in basic solutions to chloride and cyanate ions[27].

$$Cl_3\text{-}C\text{-}NH_2 + 2OH^- \longrightarrow Cl\text{-}CN + 2Cl^- + 2H_2O$$

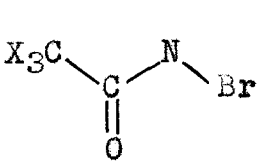
$$Cl\text{-}CN + 2OH^- \longrightarrow Cl^- + O{=}C{=}N^- + H_2O$$

Support for the reaction path is derived from the fact that in the experiments in which bromotrichloroacetamide and N-bromo-tribromoacetamide were decomposed in stronger alkaline solutions, the yield of cyanate ion were consistently and significantly larger than the yields of bromotrihalomethanes.

The fractions of molecules undergoing normal and abnormal Hofmann reaction will depend upon the magnitude of positive charge on the carbon atom and on the relative concentration of conformers LIX & LX.



(LIX)



(LX)

(X = Cl or Br)

Conformer LIX on rearrangement will yield bromotrihalomethane and cyanate while conformer LX will yield trihalomethyl isocyanate and bromide.

GLYCIDAMIDES AND GLYCIDIC ESTERS

G L Y C I D A M I D E S

Methods of Preparation of Glycidamides

Glycidamides are the amides of $\alpha:\beta$-epoxyacids. Although the parent glycidamide ($\alpha:\beta$-epoxypropionamide) itself has been prepared only recently by Payne & Williams[53], substituted glycidamides were known since long.

Substituted glycidamides have been prepared by the following methods:

(i) Condensation of aldehydes or ketones with α-haloacetamides:

This method has been used by Fourneau & co-workers[54,55], von Schick[56], Bodfross[57] and Tung, Speziale & Frazier[58] for the preparation of N-substituted glycidamides and consists in condensing aldehyde or ketone with N-substituted-α-haloacetamides in the presence of basic condensing agents. Thus, the condensation of benzaldehyde and N,N-diethyl-α-chloroacetamide in the presence of potassium t-butoxide gives N,N-diethyl-3-phenylglycidamide in 88% yield.

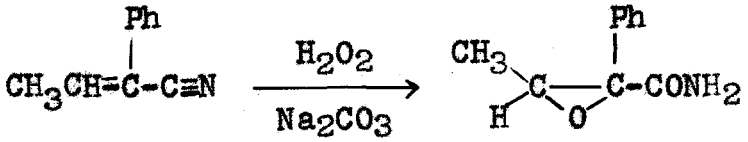
$$C_6H_5CHO + Cl\text{-}CH_2CON(C_2H_5)_2 \longrightarrow \begin{matrix} C_6H_5 \\ \diagdown \\ H \diagup \end{matrix} C \begin{matrix} \text{---} \\ O \end{matrix} CH\text{-}CON(C_2H_5)_2$$

Recently this method has also been used for the preparation of ethylenic glycidamides from ethylenic ketones

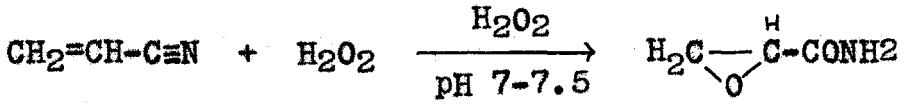
and N,N-disubstituted chloroacetamides[59].

(ii) Alkaline epoxidation of α-β-unsaturated nitriles by hydrogen peroxide

α-β Unsaturated nitriles react with excess of hydrogen peroxide and alkali or with hydrogen peroxide at controlled pH to give glycidamides[60,61,74]. Thus, α-phenyl-β-methylglycidamide has been obtained in nearly quantitative yield from the reaction of α-phenylcrotononitrile with hydrogen peroxide in the presence of sodium carbonate and aqueous acetone[60].



Reaction of equimolecular quantities of acrylonitrile and hydrogen peroxide at pH 7.0-7.5 gives glycidamide (LXI) in 66-70% yield[53].

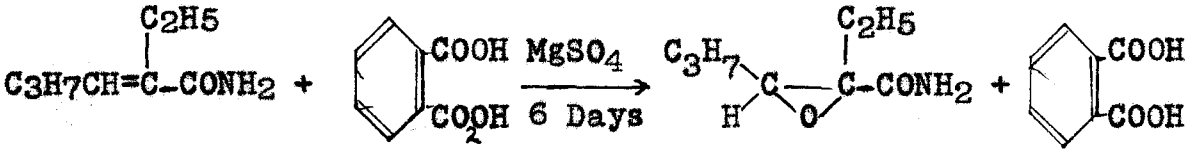


(LXI)

(iii) Peroxy-acid oxidation of α-β-unsaturated amide:

Glycidamides also result when α-β-unsaturated amides react with peroxy-acids. Thus, α-ethyl-β-propyl-glycidamide has been obtained in 69% yield by the interaction

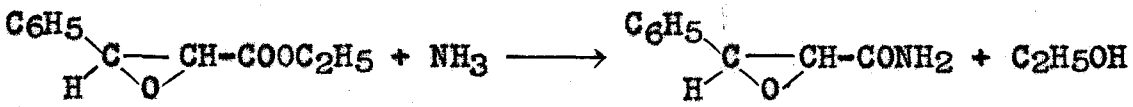
of $C_3H_7CH{=}CC_2H_5CONH_2$ and permonophthalic acid[62].



In a similar manner 2-propyl-3-ethyl-, 2,3-diethyl-, 2,3-dipropyl-, 2-methyl-3-propyl and 2-propyl-3-methylglycidamides were prepared by Shelton & Wheeler[62].

(iv) Reaction of Ammonia on Glycidic esters:

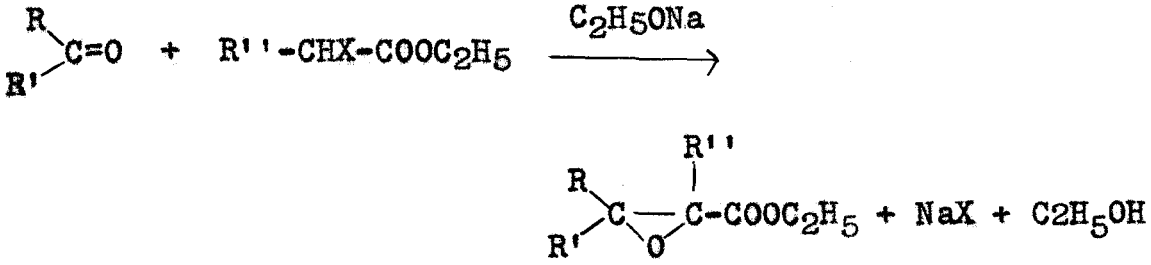
This is the most commonly employed method for the preparation of glycidamides and has been used by Fourneau & Billeter[55], Martynov & co-workers[3,63,64], Blicke & Faust[65] and others for the preparation of number of glycidamides. Glycidamides are produced by the reaction of aqueous, alcoholic or aqueous-alcoholic ammonia on glycidic esters. Thus, 3-phenylglycidamide is obtained by passing ammonia for two hours in an alcoholic solution of ethyl 3-phenylglycidate to which 30% aqueous ammonia was added before passing the ammonia gas.[55]



Methods of Preparation of Glycidic Esters

(i) Darzen's Glycidic ester condensation:

The condensation of an aldehyde or a ketone with a α-haloester in the presence of basic condensing agents to produce an α,β-epoxyester is known as Darzen's glycidic ester condensation[66].



(R,R' & R'' = H, alkyl or aryl and X = Cl or Br)

A variety of condensing agents have been used. These include sodium ethoxide[3,66], sodium amide[66], molecular sodium[67], lithium and potassium ethoxides, lithium t-butoxide, lithium pentoxide, tetramethyl-ammonium ethoxide[68] and potassium t-butoxide[69]. The use of last reagent has resulted in highly improved yields than the conventional sodium ethoxide.

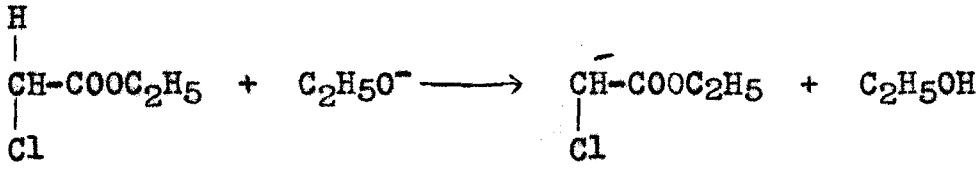
Condensations have been carried out with or without a solvent. Solvent does not have any direct effect on the yield of the product. However, there are some indirect effects which have to be considered. Aromatic

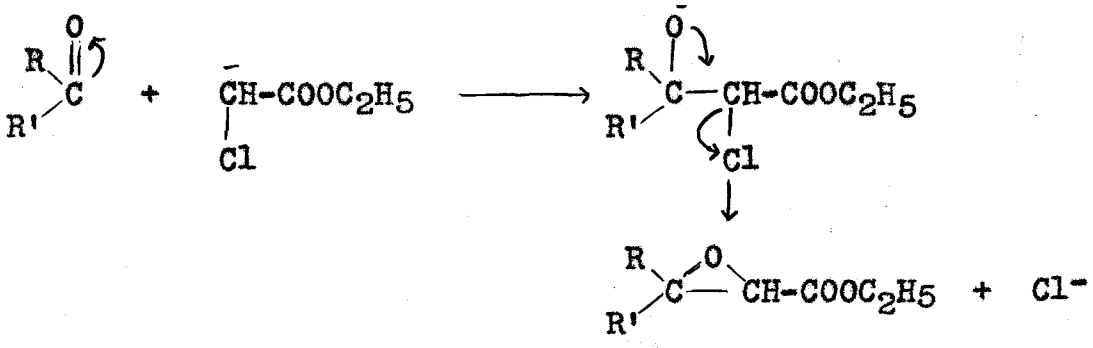
hydrocarbons like toluene, benzene or xylene have been recommended in preparations in the presence of metallic sodium. In the presence of such solvents, metallic halides formed during the course of the reaction, separates in the form of colloidal suspension and does not coat the metallic sodium[70]. Recently the use of ether has been recommended notably by Russian workers[3,63,64], in condensations involving sodium ethoxide. The removal of this solvent does not present any difficulty prior to distillation of the reaction products under reduced pressure.

The condensation is usually done under strictly anhydrous conditions and preferably in an inert atmosphere. It has been found advantageous to use 1.6 mole of the metallic alkoxide and 1.6 mole of the α-haloester to 1 mole of the aldehyde[66]. During the first stage of the reaction, the reaction mixture is kept cold. Although in one partcular case, the temperature was maintained as low as -80° [71], in most of the cases, reactions are carried out at 0-10° followed by heating to 50-60° for one or two hours towards the end. Low temperatures are specially recommended in cases where metallic sodium is used. Condensations involving metallic sodium seem to be preceded by an induction period[70] and then in some cases proceed with surpising vigour with liberation of excess of heat. Since most of the aromatic solvents that are used, are rather high boiling, this heat can not be

dissipated by reflux until the reaction temperature has risen to well over 100°, which is not advisible. At high temperatures some of the glycidic esters isomerise to ketoesters[66].

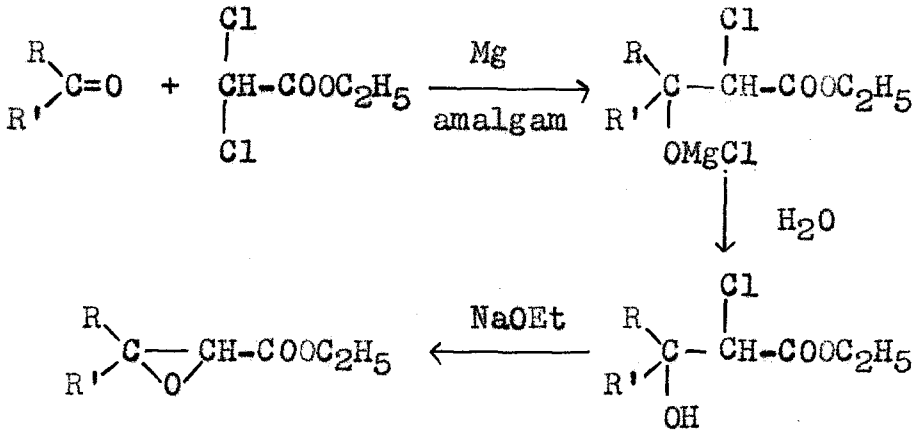
The mechanism of the glycidic ester formation probably involves the addition of the enolate of the haloester to the carbonyl group of the aldehyde or ketone followed by an intramolecular nucleophilic displacement on carbon (aldolization). Very convincing proofs for the aldolization have been provided by Ballester[72] and Zimmerman[73]. The function of basic condensing agent is to convert the haloester to its enolate ion.





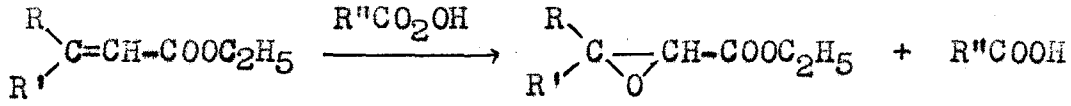
Glycidic esters have also been formed by another method also developed by Darzen[66] but not commonly employed.

It involves the reaction of aldehydes or ketones with ethyldichloroacetate and dilute magnesium amalgam. The first product of the reaction is a β-hydroxy-α-chloroester which is quantitatively converted to the glycidic ester by reaction with sodium ethoxide.



(ii) Epoxidation of α-β-unsaturated esters

Glycidic esters have also been prepared by epoxidation of esters of α,β-unsaturated acids by peracids like perbenzoic acid, peracetic acid and pertrifluoroacetic acid[75,76,77].

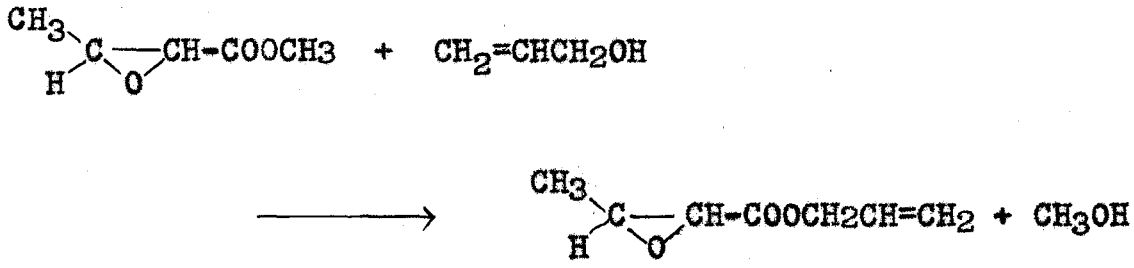


Various side reactions[75] markedly affect the yield of glycidic esters in Darzen's condensation. These side reaction include aldol condensation in the case of

alkanals, self condensation of ketones and the alkylation of the enolate of ketones by haloester. Moreover, ∝-arylglycidic esters do not result from condensations attempted with carbonyl compounds having ∝ -hydrogen and∝ -aryl-∝-haloesters, for example glycidic esters are not formed when condensations are carried out with ∝ -chloro- or bromo-phenylesters and acetone, cyclohexanone or acetophenone[78]. Use of peracids do not present these difficulties and the yields reported are very high. In addition, this method provides a way of ascertaining the extent of progress of reaction at any given time by conventional iodometric technique[75].

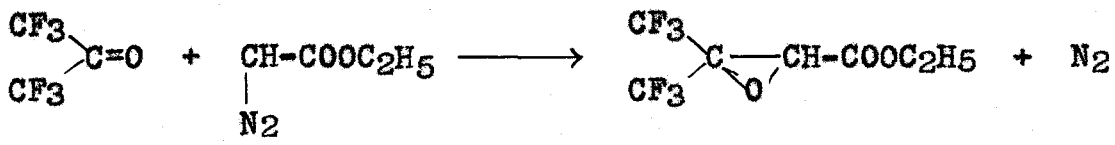
(iii) Ester exchange reaction

The alkyl group of the ester component of the glycidic ester may be exchanged without destruction of the oxirane ring, with alkyl group of saturated or unsaturated alcohols in the presence of catalysts and under mild conditions. This ester exchange reaction has been used for the preparation of certain unsaturated glycidic esters and diepoxides which are not easily obtained by other routes. Thus, methyl 2,3-epoxybutyrate undergoes exchange reaction with allyl alcohol in the presence of sodium to give allyl 2,3-epoxybutyrate[79].



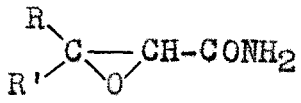
(IV) Condensations with diazoacetic esters

Recently glycidic esters have been prepared by Gambaryan & co-workers[80] by condensation of perfluoro ketones and diazoacetic esters. Thus, the condensation of perfluroacetone and ethyl diazoacetate gives ethyl 3,3-di(trifluoromethyl)glycidate in 82% yield.

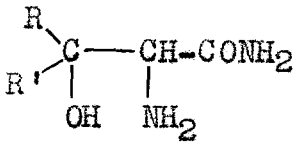


Reaction of Ammonia on Glycidic Esters

Depending on the reaction conditions, glycidic esters yield glycidamides (LXII) or amides of hydroxy amino acids (LXIII) on reaction with ammonia[3,63,64,66].



(LXII)



(LXIII)

The reaction with ammonia takes place in two stages. First the amides of glycidic acids are formed and these further react with opening of the epoxide ring, resulting in the formation of amides of hydroxy amino acids. Replacement of the ester group by amide group proceed with much greater facility than the opening of the epoxide ring, so that the reaction can always be stopped at the stage of formation of glycidamides. This is partcularly easily effected in glycidic esters having large substituents at the β position. Steric hindrance of the large substituents markedly lowers the reactivity of the epoxide ring. In practice amides are easily obtained at room temperature if the mixture of glycidic esters and aqueous, alcoholic or aqueous-alcoholic ammonia is left overnight. The reaction time varies with individual glycidic esters. Ammonium salts sometimes result if

reaction of glycidic ester is carried out at an elevated temperature[3].

The positions of the hydroxy and amino groups in the hydroxy amino amides (formed by the opening of the epoxide) appears to be in doubt. Fourneau & Billeter[55] report that if ammonia and aliphatic amines are used, α-hydroxy-β-aminoamides are obtained, whereas with aromatic amines reverse orientation results. The results of these workers have been corroborated by Martynov & co-workers [3] in their earlier work with β,β-disubstitutedglycidic esters and ammonia, the reaction product being α-hydroxy-β-amino-amides. In a subsequent publication[63], they claim that β-phenylglycidic ester and all substituted β-phenylglycidic esters having electron donating substituents in the aromatic ring, add ammonia and aromatic amines at the α carbon and not at the β carbon as claimed by Fourneau & Billeter[55].

It appears that more work is required before any generalisation can be made or the structure of such amino hydroxy compounds formed, by the ring opening of the glycidic esters, can be assigned by analogy. Eliel[81] has called attention to the confusion that sometimes arises in the study and interpretations of the opening of unsymmetrical epoxides due to contradictory experimental results. The reasons that he has listed for this state of

affair include difficulties in separating and analysing the two isomeric products, rearrangements occurring during the synthesis of authentic specimens of possible isomeric products and sensitiveness of the product ratio to minor changes in the reaction conditions. To the above list Cohen and co-workers[82] have added one more that is the possibility of the rearrangement of the initially formed product to its isomer.

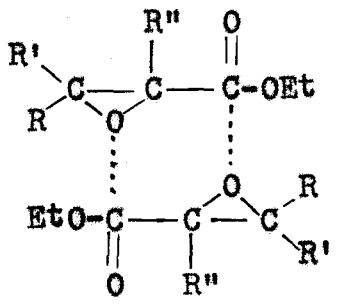
Parker & Issacs[83] also point out the direct contradiction between the results of various investigators and to the fact that the position of attack in all the reactions (opening of the epoxide in general) has been determined only by the isolation of one reaction product sometimes in very low yield and as such necessiating further work before any definite conclusion can be reached.

Infra-red and N.M.R.

Spectra of Glycidic Esters and Glycidamides

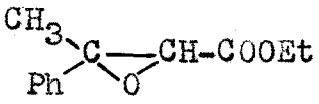
Infra-red spectra of glycidic esters

Morris & Young[84] have shown from the study of infra-red spectra of various glycidic esters that the glycidic esters show two absorption bands of almost equal intensity in the 1700-1800 cm^{-1} carbonyl stretching region in non hydrogen bonding solvents like carbon tetrachloride, carbon disulphide, benzene, cyclohexane and 2-nitropropane etc. The average absorption being at 1729 and 1753 cm^{-1}. However, if hydrogen bonding solvent like chloroform, n-butyl alcohol, aniline methanol or n-cresol are used, the two bands are replaced by a single rather broad band at about 1737 cm^{-1}. They have attributed the duplicate bands to dimer formation which permits coupling of the two carbonyl stretching vibrations.

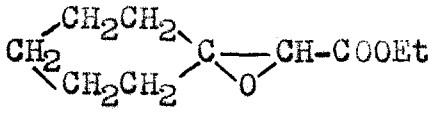


House & Blacker [85] have also studied a number of infra-red spectra of glycidic esters. They have corroborated

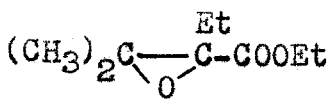
the findings of Morris and Young that glycidic esters show two bands in the 1700-1800 cm^{-1} region. However, they have observed that the two bands are not replaced by a single band when infra-red spectra are recorded in chloroform. Infra-red spectra of glycidic esters LXIV, LXV and LXVI in chloroform showed that the two bands ~~are~~ were still present.



(LXIV)



(LXV)



(LXVI)

They also do not agree with Morris & Young's suggestion that the two bands are due to dimers and have proposed that the two bands are due to rotational isomers.

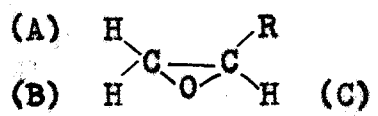
Infra-red spectra of glycidamides

Tung & co-workers[58,86] have studied the infra-red spectra of glycidamides. They have shown that in the infra-red spectra of epoxyamides, the bands attributed to epoxy group are in the 1250, 909 and 833 cm^{-1} regions. In the trans isomer the band at 833 cm^{-1} is absent although it is present in the cis epoxyamide.

N.M.R. spectra of glycidic esters and glycidamides

Nuclear magnetic resonance spectra of glycidic esters have not been reported in the literature and are

recorded here for the first time. Tung and co-workers[58] have recently reported the N.M.R. spectral data for cis and trans glycidamides. They have reported the coupling constants for α ,β hydrogens ($J_{H_\alpha}J_{H_\beta}$) in the cis epoxyamide to be 5.0 c.p.s. and for the trans isomer ($JH_\alpha JH_\beta$) to be 2.0 c.p.s. They have corelated the values of coupling constants with the values reported earlier by Reilly & Swalen[87] for the simple epoxy compounds (LXVII a,b,c & d) of the following types;



(A) (B) (C)

(LXVII)

a. R = COOH

b. R = CN

c. R = C_6H_5

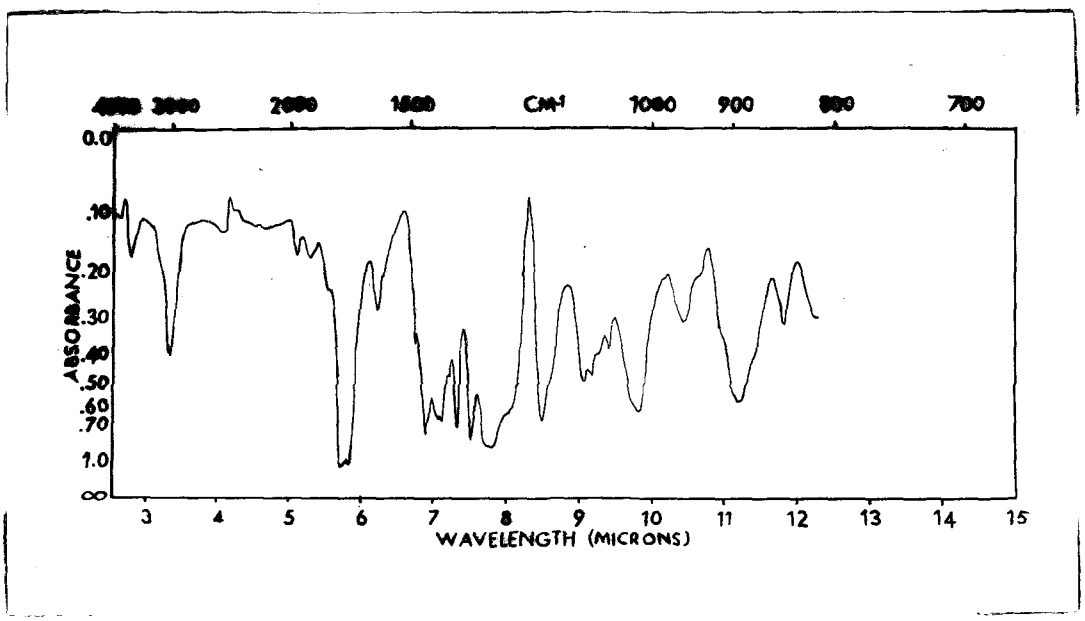
d. R = CH_3CO

The coupling constants reported by Reilly & Swalen were approximately the same in all the four molecules with J_{AB} = 5.8 J_{AC} = 2.2 and JBC = 4.6 .

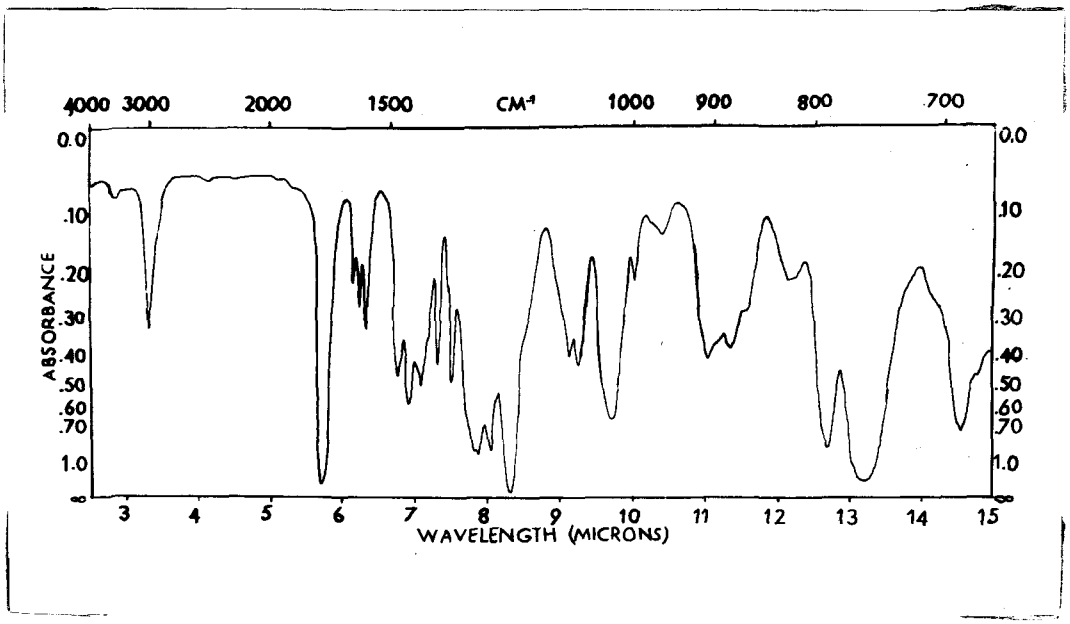
PRESENT WORK AND DISCUSSION

PRESENT WORK AND DISCUSSION

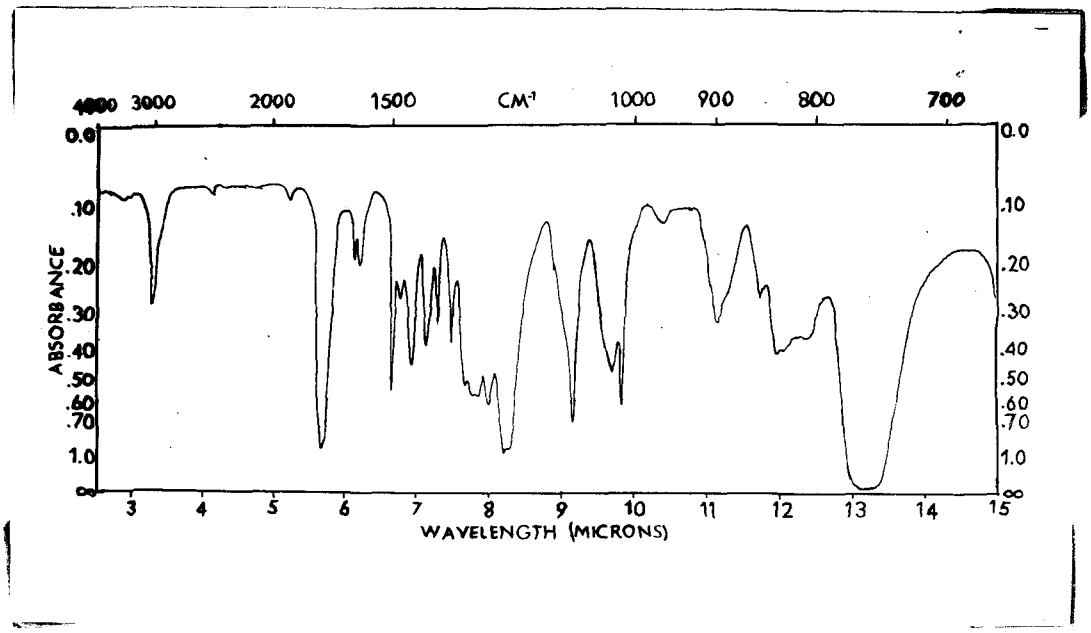
Glycidamides used in the present work were prepared by the action of ammonia on glycidic esters. Glycidic esters were prepared by Darzen's method. The infra-red spectra of ethyl 3-phenylglycidate (fig-1) and ethyl 3-(o-chlorophenyl)-glycidate in chloroform show two bands at 1725 & 1750 cm^{-1} in agreement with the published data[84,85]. However, the infra-red spectra (recorded on Perkin-Elmer Infracord 137 in chloroform) of ethyl-3-(m-chlorophenyl)glycidate (fig-2), ethyl 3-(p-chlorophenyl)glycidate (fig-3) and ethyl 2-methyl-3-(p-chlorophenyl)glycidate (fig-4) do not show the characterstic double bands of glycidic esters in the 1700-1800 cm^{-1} region.



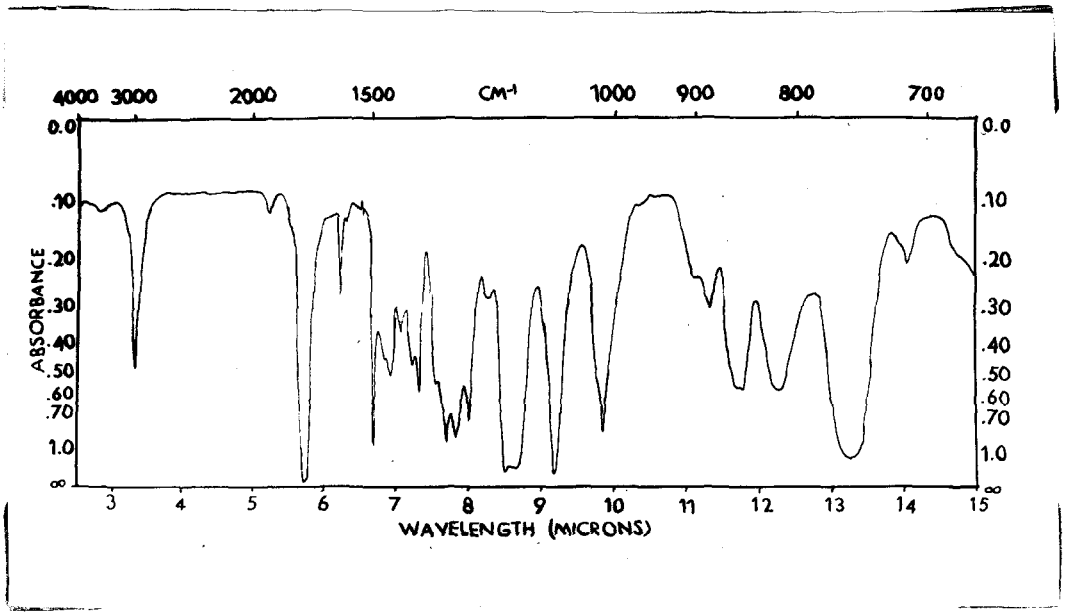
(Fig-1)


4000 3000 2000 1500 CM-1 1000 900 800 700
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

(Fig-2)


3000 2000 1500 CM-1 1000 900 800 700
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

(Fig-3)

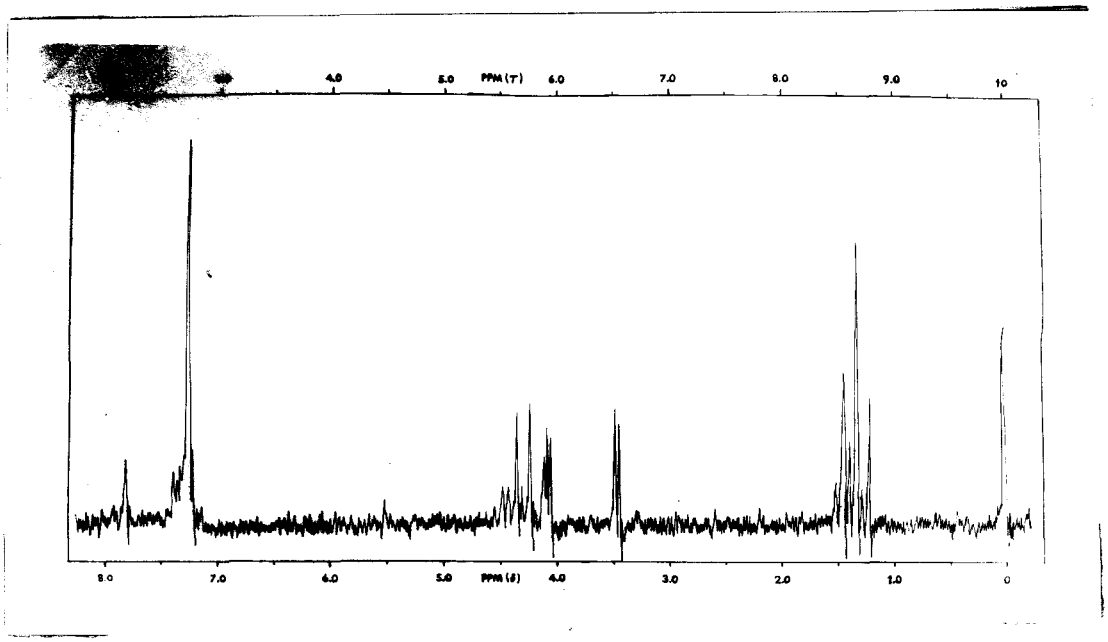


(Fig-4)

All the three above mentioned glycidic esters show a single band at 1750 cm^{-1}. Since the amides of 3-(m-chlorophenyl)-, 3-(p-chlorophenyl)-, 2-methyl-3-(p-chlorophenyl)- and 3-(p-toluyl)glycidic esters are not reported in the literature, in order to ascertain that the starting compounds were actually glycidic esters, n.m.r. spectra of these glycidic esters were recorded and compared with n.m.r. spectra of ethyl 3-phenylglycidate and ethyl 3-(o-chlorophenyl)glycidate.

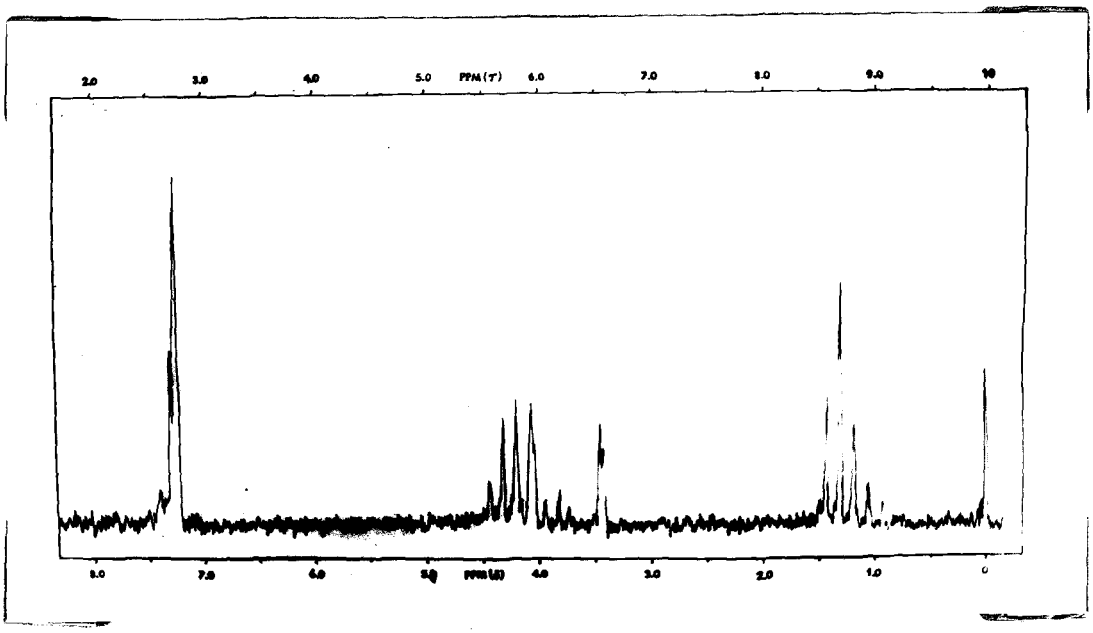
Ethyl 3-phenylglycidate and 3-phenylglycidamide are reported in the literature. The boiling point of the ethyl 3-phenylglycidate and melting point of 3-phenylglycidamide prepared during the course of present work agreed with the

the reported values[55]. Ethyl 3-(o-chlorophenyl)glycidate is not reported in the literature and was prepared for the first time. The infra-red spectrum of ethyl 3-(o-chlorophenyl)glycidate shows characterstic absorption of glycidic esters (two bands in 1700-1800 cm^{-1} region). The melting point of ethyl 2,3-diphenyl-glycidate (59-60°) and 2,3-diphenylglycidamide (133-4°) prepared during present work agreed with reported values[104,53]. Therefore all the above mentioned glycidic esters are definitely glycidic esters. On comparison it was observed that the n.m.r. spectra (recorded on Varian associates 60 MC spectrometer in deutero-chloroform with tetramethylsilane as internal reference) of ethyl

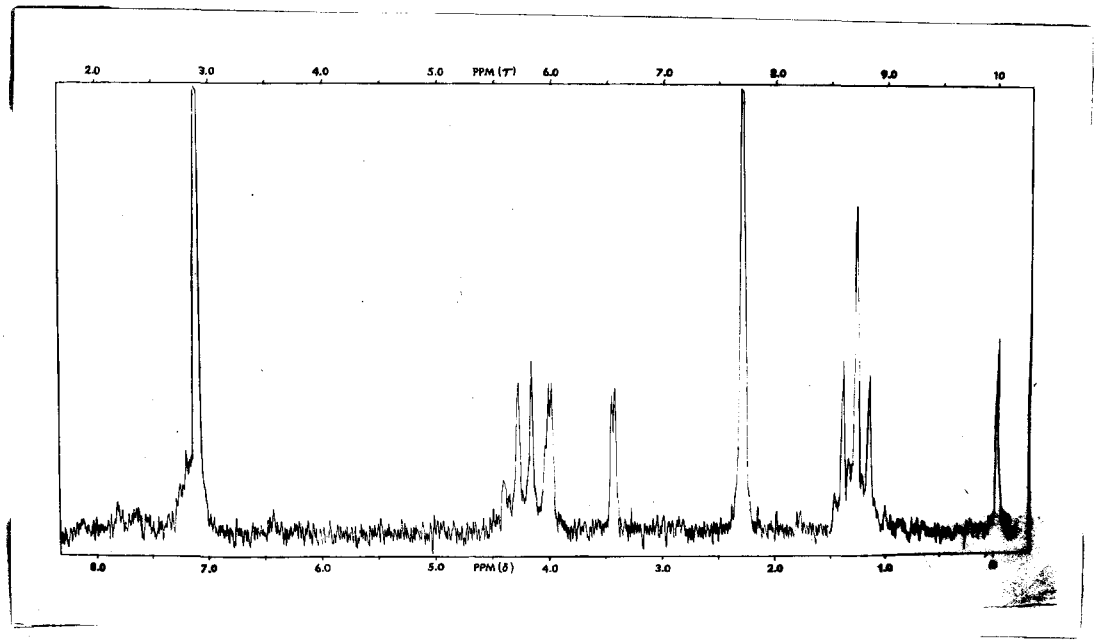


(Fig-5)

3-(m-chlorophenyl)glycidate (fig-5), ethyl 3-(p-chlorophenyl)-glycidate (fig-6) and ethyl 3-(p-toluyl)glycidate (fig-7) were found to be similar to the n.m.r. spectra of ethyl 3-phenylglycidate (fig-8) and ethyl 3-(o-chlorophenyl)glycidate (fig-9). The n.m.r. spectrum of 2,3-diphenylglycidic ester (fig-10) was different from the n.m.r. spectra of other glycidic esters as it contained a phenyl group at the α- carbon atom. The n.m.r. spectrum of ethyl 2-methyl-3-(p-chlorophenyl)-glycidate was also different from the n.m.r. spectra of other glycidic esters. It is possible that the glycidic ester prepared by the condensation of p-chlorobenzaldehyde and ethyl α-bromopropionate, was not pure. This is supported by the observation that the yield of glycidamide prepared from this



(Fig-6)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3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
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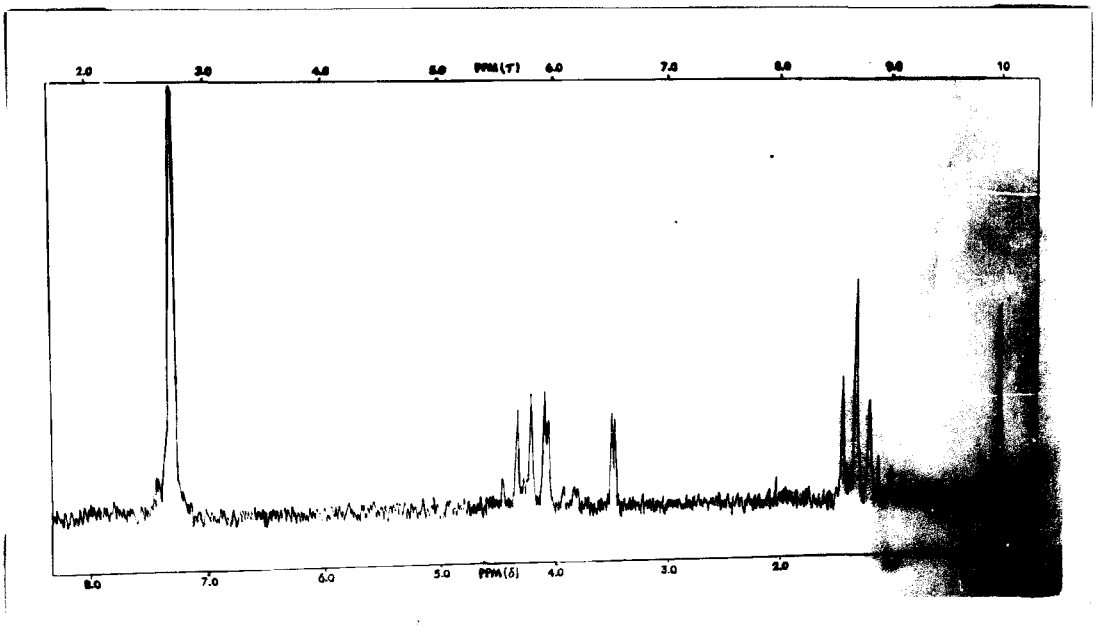
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0

(Fig-7)


2.0
3.0
4.0
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PPM(τ)
6.0
7.0
8.0
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10
8.0
7.0
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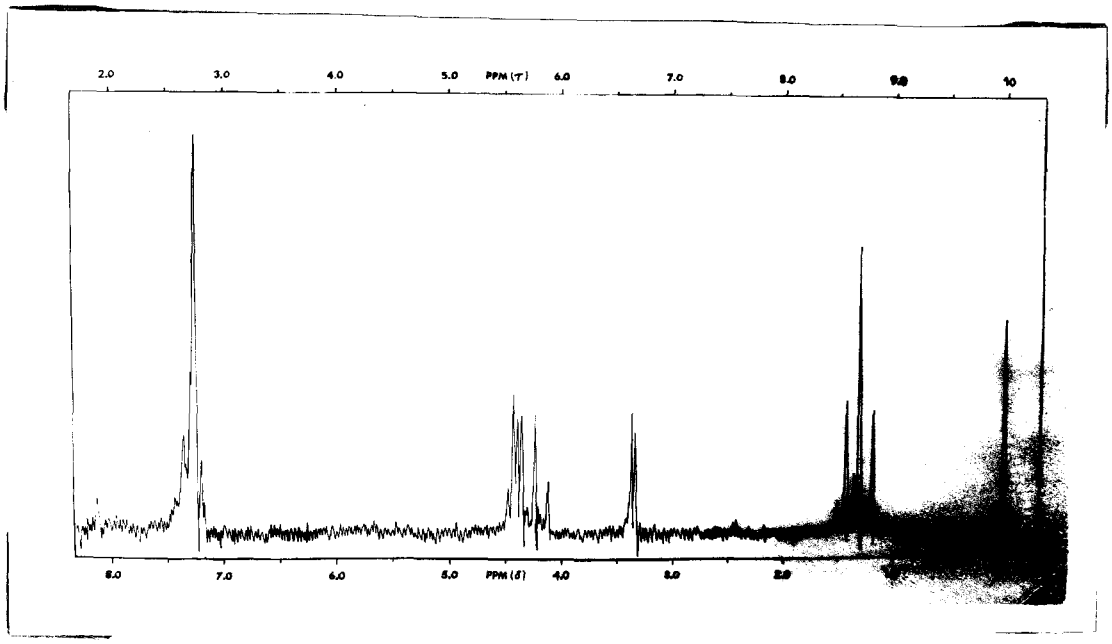
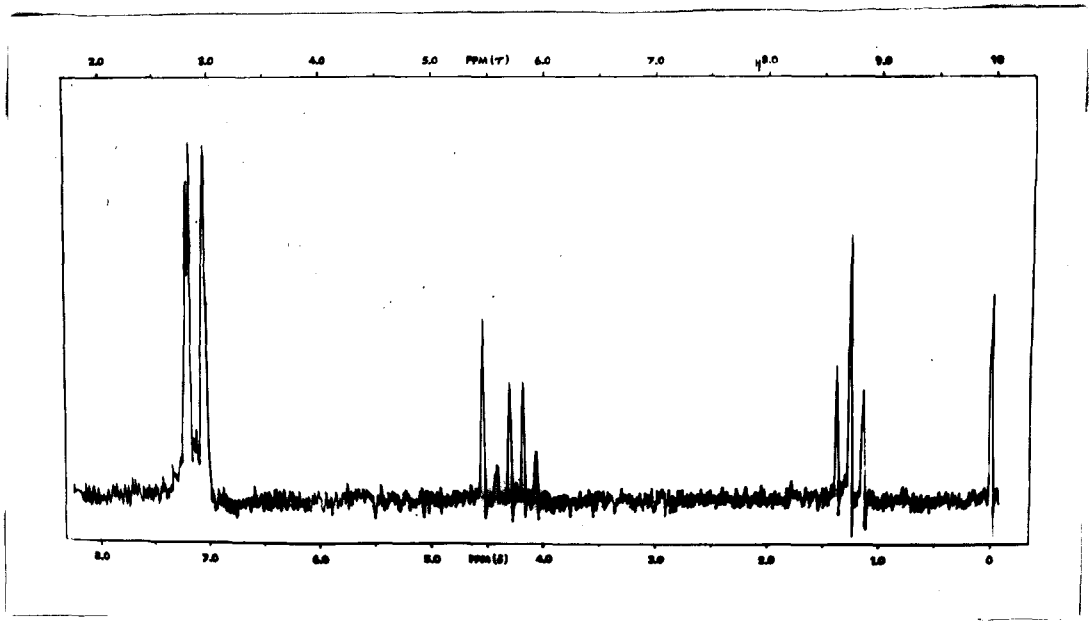
5.0
PPM(δ)
4.0
3.0
2.0

(Fig-8)


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0

(Fig-9)

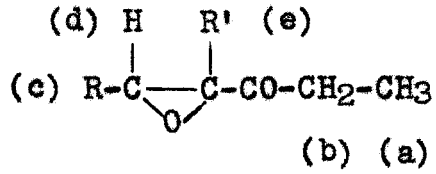

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

(Fig-10)

glycidic ester was poor (cf. p 138).

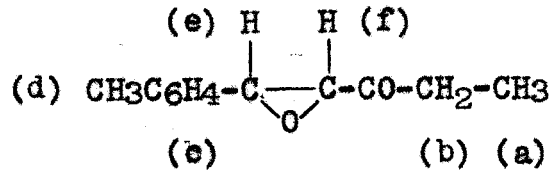
The following table gives the n.m.r. spectral data chemical shift in PPM (δ) of glycidic esters.

Table



No	Compound	a	b	c	d	e
1.	R = H R' = C_6H_5	1.32	4.23	7.3	3.47 or 3.50	3.50 or 3.47
2.	R = H R' = o-ClC_6H_4	1.33	4.32	7.24	3.34 or 3.38	3.38 or 3.34
3.	R = H R' = m-ClC_6H_4	1.32	4.22	7.23	3.48 or 3.44	3.44 or 3.48
4.	R = H R' = p-ClC_6H_4	1.32	4.20	7.25	3.42 or 3.45	3.45 or 3.42
5.	R = C_6H_5 R' = C_6H_5	1.27	4.22	7.05 or 7.17	4.54	7.17 or 7.05

6.

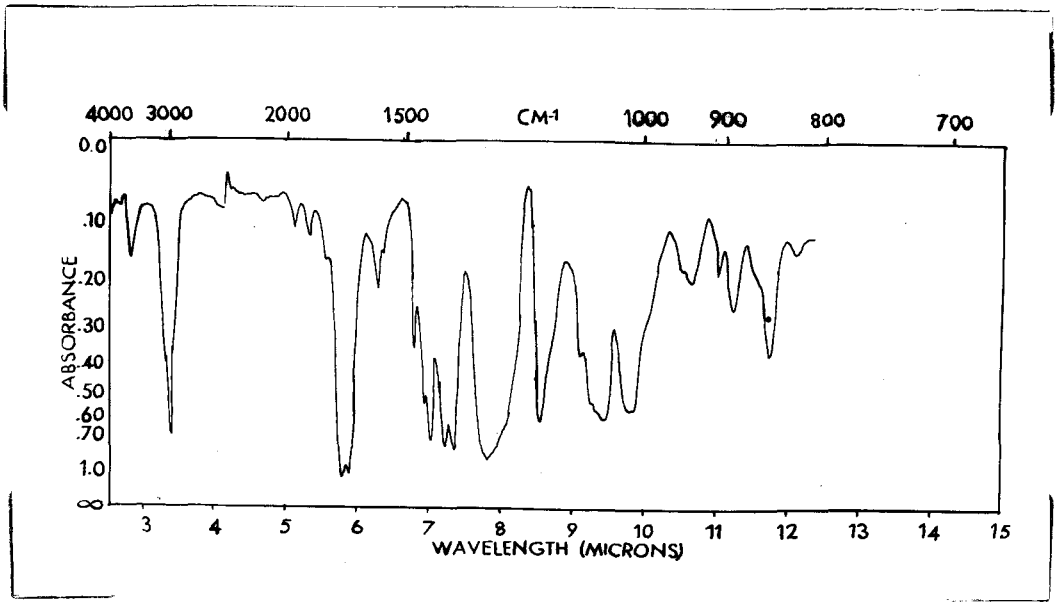


a	b	c	d	e	f
1.32	4.20	7.15	2.30	3.44 or 3.47	3.47 or 3.44

The n.m.r. spectra of glycidic esters are not reported in the literature. The published work on n.m.r. spectra of N-substituted glycidamides[58] report doublets for α and β hydrogens. In the n.m.r. spectra of glycidic esters given above, it will be observed that doublets are not obtained for the α and β hydrogens. It is possible that the doublets obtained by Tung and co-workers[58] for α , β hydrogens may be due to higher resolution.

The melting point of 3-(m-nitrophenyl)glycidamide (163-4°) prepared during the course of present work was found to be different from the reported value i.e. 180-1° [64]. However as analysis of the amide agreed with molecular formula and the melting point of ethyl 3-(m-nitrophenyl)glycidate (54-55°) agreed with one of the two reported values i.e. 55.5° [64] & 58° [88], the compound prepared from ethyl 3-(m-nitrophenyl)glycidate by reaction with ammonia may be presumed to be 3-(m-nitrophenyl)glycidamide.

The melting point of 3-methyl-3-phenylglycidamide (167-8°) was also found to be different from the reported value i.e. 157-8° [3]. The infra-red spectrum of ethyl 3-methyl-3-phenyl glycidate (fig-11) shows two bands characterstic of glycidic esters in the 1700-1800 cm^{-1} region. Therefore, the amide prepared from ethyl 3-methyl-3-phenyl-glycidate may be presumed to be 3-methyl-3-phenylglycidamide.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0.0
.10
.20
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.40
.50
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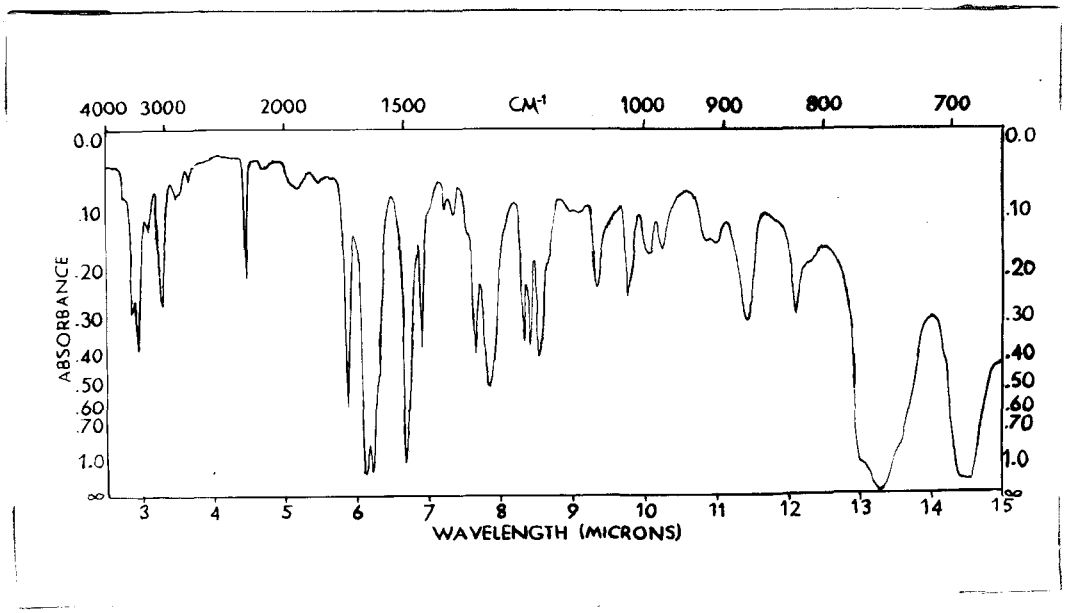
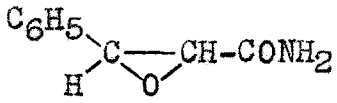
1.0
∞
ABSORBANCE
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

(Fig-11)

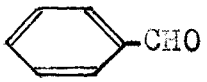

4000 3000 2000 1500 CM-1 1000 900 800 700
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

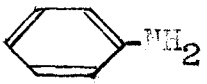
(Fig-12)

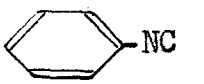
3-Phenylglycidamide (LXVIII) was subjected to Hofmann reaction with bromine and alkali. Steam distillation of the reaction mixture gave benzaldehyde (LXIX), aniline (LXX) and phenylisocyanide (LXXI). Benzaldehyde was characterised by preparation of its phenylhydrazone and 2:4-dinitrophenylhydrazone. The analysis and melting point of phenylhydrazone agreed with the analysis and melting point of the authentic specimen (phenylhydrazone of benzaldehyde). The analysis, melting point and infra-red spectrum of 2:4-dinitrophenylhydrazone also agreed with the analysis, melting point and infra-red spectrum of authentic specimen (2:4-dinitrophenylhydrazone of benzaldehyde). Aniline was identified by preparation of the benzoyl derivative and comparison with benzanilide. The analysis, melting point and infra-red spectrum of the benzoyl derivative agreed with the analysis, melting point and infra-red spectrum of benzanilide. Phenylisocyanide

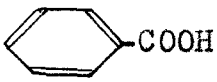


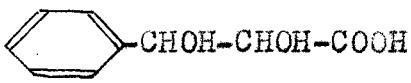
(LXVIII)

(LXIX) 

(LXX) 

(LXXI) 

(LXXII) 

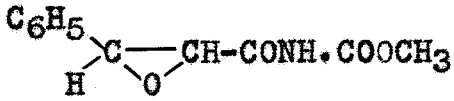
(LXXIII) 

was identified by infra-red spectrum (fig-12) which shows characterstic isocyanide absorption at 2250 cm^{-1} [89,90] and by hydrolysis of the isocyanide after removing aniline(also obtained in the reaction) by treatment with 4% hydrochloric acid. The amine obtained after hydrolysis could be diazotised and coupled with β-naphthol (alkaline), showing the presence of primary aromatic amine. The amine was benzoylated. The melting point of the benzoyl derivative corresponded with that of benzanilide and mixed melting point did not show any depression.

The residue left after steam distillation gave no non acid product. Benzoic acid (LXII) and erythro β-phenylglyceric acid (LXXIII) were obtained on acidification of the residue. Benzoic acid was identified by mixed melting point which was not depressed, with authentic specimen. Erythro β-phenylglyceric acid was characterised by its melting point i.e. 122° (reported[91,92,125] 122°) and conversion to methyl ester m.p. 87° (reported[91] 87°) and dibenzoyl derivative m.p. 187° (reported[91] 187°). The acid gave positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid[93]. Acid hydrolysis of ethyl 3-phenylglycidate by the method of Blicke & Faust[65] (who obtained β, β-diphenylglyceric acid by acid hydrolysis of ethyl β, β-diphenylglycidate) gave the threo isomer of β-phenylglyceric acid m.p. 141° (reported[91,125] 141°)

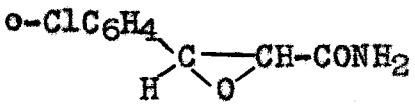
Hofmann reaction of 3-phenylglycidamide under

special conditions using sodium methoxide and bromine in methanol did not give the expected urethane (LXXIV)

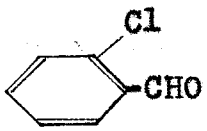


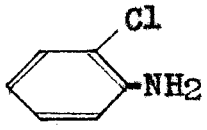
(LXXIV)

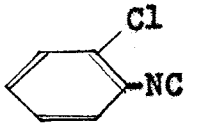
Hofmann reaction of 3-(o-chlorophenyl)glycidamide (LXXV) gave o-chlorobenzaldehyde (LXXVI), o-chloroaniline (LXXVII) and o-chlorophenylisocyanide (LXXVIII) as the steam volatile products. o-Chlorobenzaldehyde was identified by preparation of 2;4-dinitrophenylhydrazone and mixed melting point determination which showed no depression with the 2;4-dinitrophenylhydrazone of o-chlorobenzaldehyde. o-Chloroaniline was identified by preparation of the benzoyl

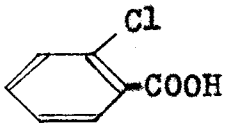


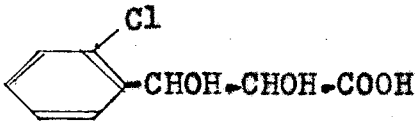
(LXXV)

(LXXVI) 

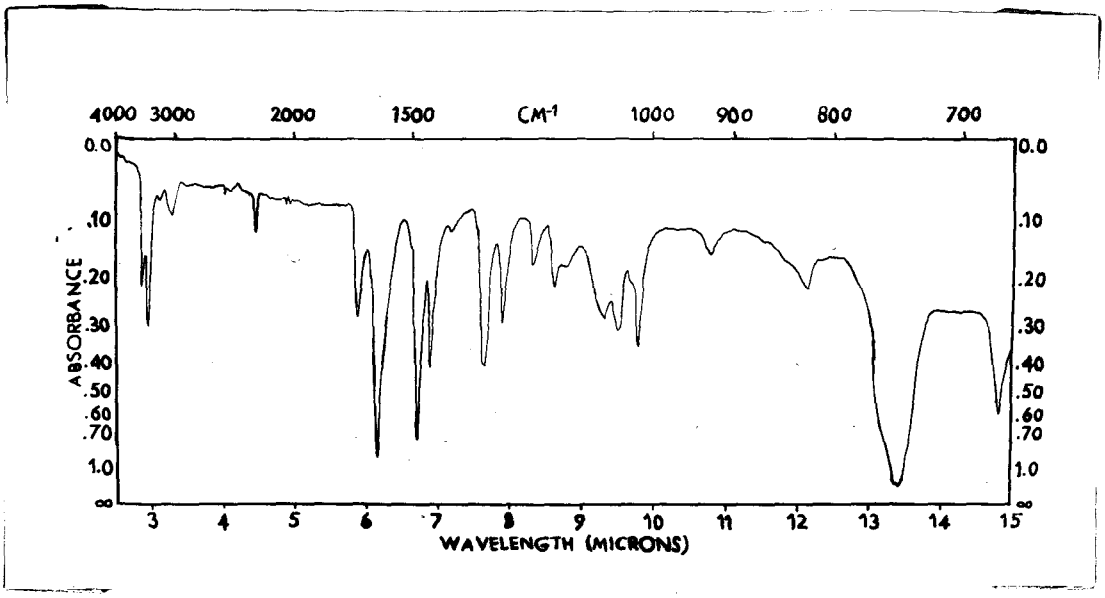
(LXXVII) 

(LXXVIII) 

(LXXIX) 

(LXXX) 

derivative and determination of mixed melting point which showed no depression with benzoyl derivative of o-chloroaniline. o-Chlorophenylisocyanide was identified by infra-red spectrum (fig-13) which showed characterstic absorption for the isocyanide group at 2250 cm^{-1} [89,90]. As the quantity of isocyanide formed in the reaction was very little, it could not be characterised directly by hydrolysis and preparation of the benzoyl derivative after washing away o-chloroaniline with 4% hydrochloric acid as was done in the characterisation of phenylisocyanide in the Hofmann reaction of 3-phenylglycidamide. However, by analogy with the formation of phenylisocyanide in the Hofmann reaction of 3-phenylglycidamide and isolation of o-chloroaniline in the reaction, it may be presumed that the isocyanide formed in the reaction is o-chlorophenylisocyanide. No non acid product was obtained from the residue left after steam distillation. o-Chlorobenzoic acid (LXXIX) and erythro β-(o-chlorophenyl)glyceric acid (LXXX) were obtained on acidification of the residue. o-Chlorobenzoic acid was identified by mixed melting point which was not depressed with authentic specimen. Alkaline hydrolysis of ethyl 3-(o-chlorophenyl)glycidate gave an hydroxy acid m.p. 139°. Erythro β-(o-chlorophenyl)glyceric acid was characterised by positive test shown by it with guaiacol and conc. sulphuric acid and mixed melting point which showed no depression with the acid obtained by the hydrolysis of ethyl 3-(o-chlorophenyl)glycidate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.20
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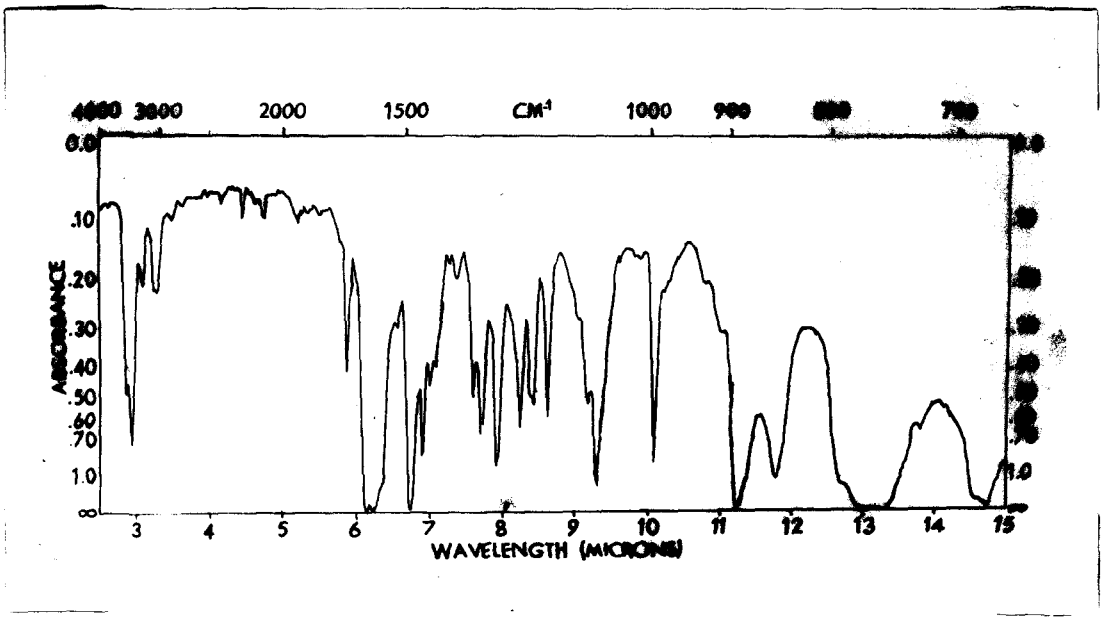
1.0
∞
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

(Fig-13)


2000 1500 CM-1 1000
ABSORBANCE
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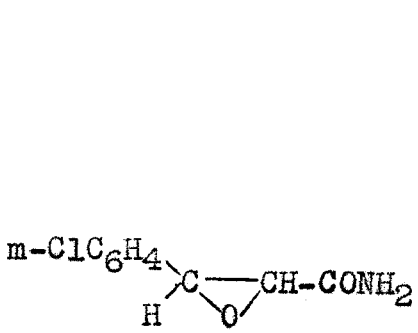
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

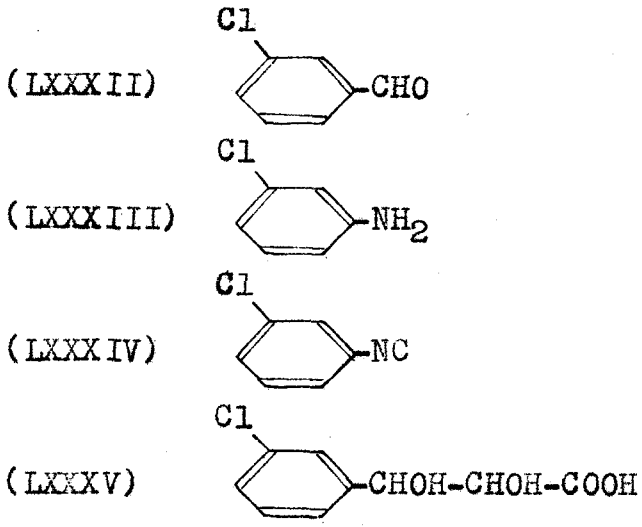
(Fig-14)

English and Heywood[94] obtained erythro α,β-dihydroxycaproic acid by alkaline hydrolysis of ethyl α,β-epoxycaproate. By analogy, the acid obtained by alkaline hydrolysis of ethyl 3-(o-chlorophenyl)glycidate and the acid isolated in the Hofmann reaction are assigned the erythro configuration. The analysis of the hydroxy acid isolated in the Hofmann reaction also agreed with the molecular formula of β-(o-chlorophenyl)-glyceric acid. Acid hydrolysis of ethyl 3-(o-chlorophenyl)-glycidate by the method of Blicke & Faust[65] gave another hydroxy acid m.p. 207-8° which gave positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid[93] and the analysis agreed with the molecular formula of β-(o-chlorophenyl)glyceric acid. By analogy with the obtention of threo β-phenylglyceric acid by acid hydrolysis of ethyl 3-phenylglycidate, the acid m.p. 207-8° is assigned the threo configuration. Alkaline hydrolysis of 3-(o-chlorophenyl)glycidamide yielded the dihydroxy acid m.p. 207-8° (threo isomer). Mixed melting point with the acid obtained by acid hydrolysis of ethyl 3-(o-chlorophenyl)-glycidate was undepressed.

Hofmann reaction of 3-(m-chlorophenyl)glycidamide (LXXXI) gave m-chlorobenzaldehyde (LXXXII), m-chloroaniline (LXXXIII) and m-chlorophenylisocyanide (LXXXIV) as the steam volatile products. m-Chlorobenzaldehyde was identified by preparation of 2:4-dinitrophenylhydrazone and mixed melting



(LXXXI)

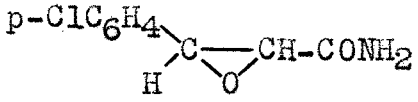


(LXXXII) (LXXXIII) (LXXXIV) (LXXXV)

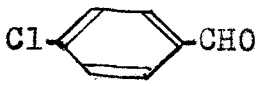
determination which showed no depression, with authentic specimen (2:4-dinitrophenylhydrazone of m-chlorobenzaldehyde). m-Chloroaniline was identified by preparation of its benzoyl derivative and determination of mixed melting point which was not depressed with the benzoyl derivative of m.chloroaniline. The infra-red spectrum of the steam volatile products (fig-14) shows characterstic isocyanide absorption band at 2250 cm^{-1} [89,90]. By analogy with the formation of phenylisocyanide in the Hofmann reaction of 3-phenylglycidamide, the isocyanide formed in the Hofmann reaction of 3-(m-chlorophenyl)glycidamide may be presumed to be m-chlorophenylisocyanide. No non acid product was obtained from the residue left after steam distillation. Acidification of the residue with conc. hydrochloric acid gave an acid m.p. 118-20° which gave positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid[93] and mixed melting point determination with the hydroxy

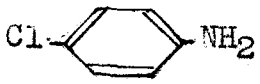
acid obtained by alkaline hydrolysis of ethyl 3-(m-chlorophenyl)glycidate showed no depression. On the basis of these two tests and by analogy with the formation of erythro β-phenylglyceric acid and erythro β-(o-chlorophenyl)glyceric acid in the Hofmann reaction of 3-phenylglycidamide and 3-(o-chlorophenyl)glycidamide respectively, the acid m.p. 118-20° is characterised as erythro β-(m-chlorophenyl)glyceric acid (LXXXV).

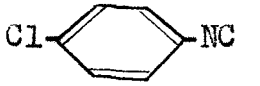
Steam distillation of the reaction mixture after Hofmann reaction of 3-(p-chlorophenyl)glycidamide (LXXXVI) gave p-chlorobenzaldehyde (LXXXVII), p-chloroaniline (LXXXVIII) and p-chlorophenylisocyanide (LXXXIX). p-Chlorobenzadehyde was identified by preparation of 2:4-dinitrophenylhydrazone and mixed melting point which showed no depression with 2:4-dinitrophenylhydrazone of p-chlorobenzaldehyde. p-Chloroaniline was identified by preparation of benzoyl



(LXXXVI)

(LXXXVII) 

(LXXXVIII) 

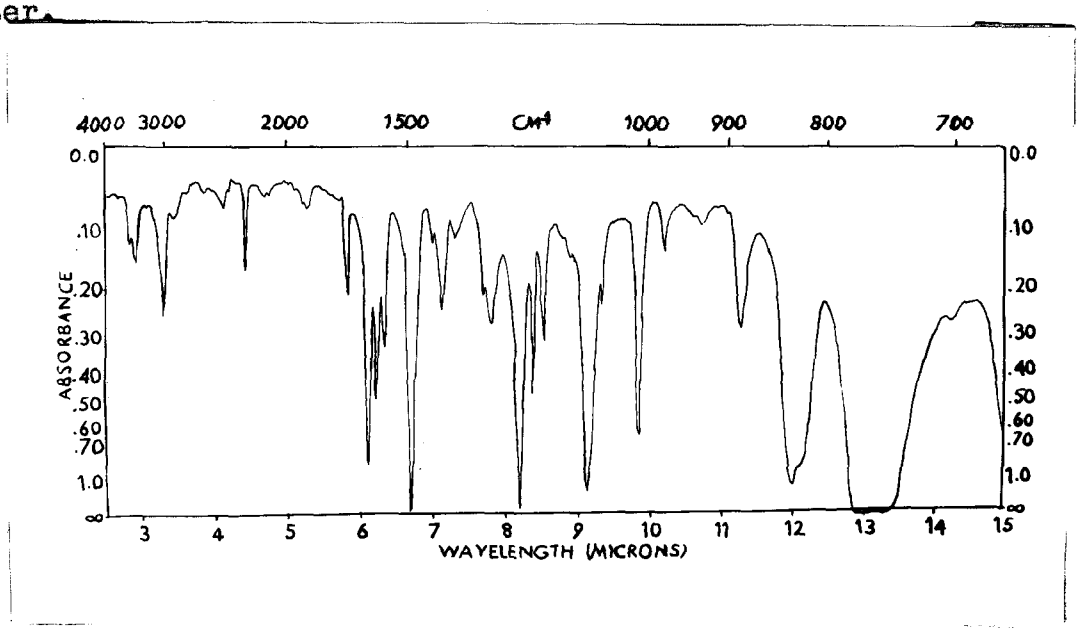
(LXXXIX) 

(XC) 

(XCI) 

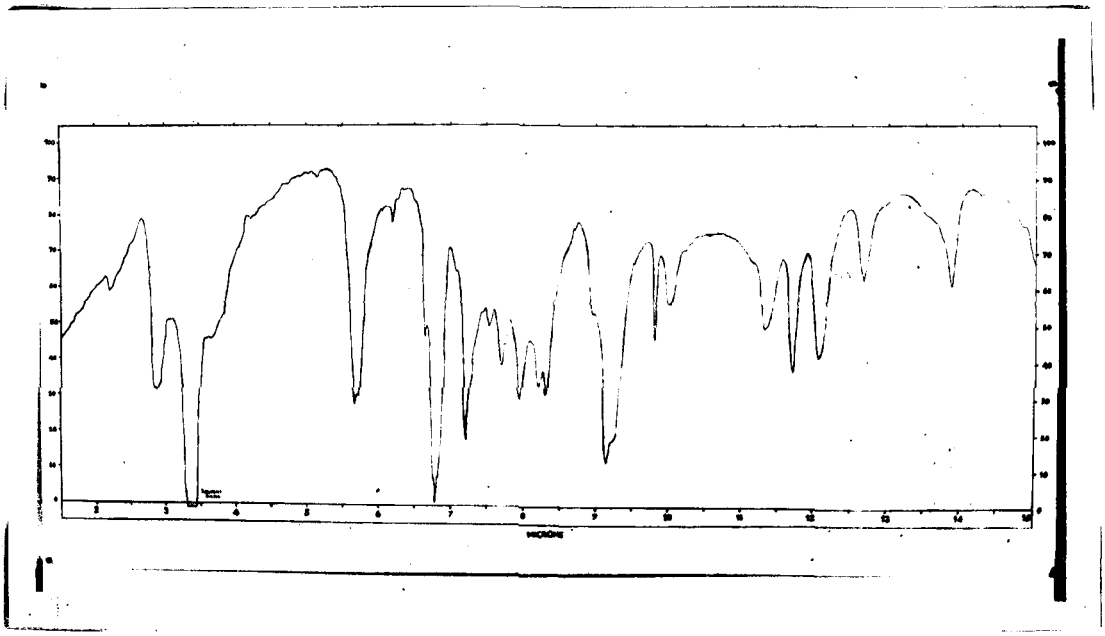
derivative and determination of mixed melting point which showed no depression with benzoyl derivative of p-chloroaniline. Infra-red spectrum (fig-15) of steam volatile products of Hofmann reaction of 3-(p-chlorophenyl)glycidamide shows a band characterstic of isocyanide group at 2250 cm^{-1} [89,90]. By analogy with the formation of phenylisocyanide in the Hofmann reaction of 3-phenylglycidamide, the isocyanide formed in the Hofmann reaction of 3-(p-chlorophenyl)glycidamide may be presumed to be p-chlorophenylisocyanide. No non acid product was obtained from the resiue left after steam distillation. Acidification of the residue gave p-chlorobenzoic acid (XC) and erythro β-(p-chlorophenyl)glyceric acid (XCI). p-Chlorobenzoic acid was identified by mixed melting point which was not depressed with authentic specimen. Alkaline hydrolysis of ethyl 3-(p-chlorophenyl)glycidate by the method of English & Heywood [94] gave an acid m.p. 122-4°. The analysis of the acid agreed with the molecular formula of β-(p-chlorophenyl)glyceric acid. The acid m.p. 121-23° obtained in the Hofmann reaction of 3-(p-chlorophenyl)-glycidamide, showed positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid[93] and mixed melting point with the hydroxy acid obtained by alkaline hydrolysis 3-(p-chlorophenyl)glycidamide was undepressed. On the basis of these tests the acid m.p. 121-3° is characterised as erythro β-(p-chlorophenyl)glyceric acid.

The infra-red spectrum (fig-16) of erythro β-(p-chlorophenyl)-glyceric acid was similar to the infra-red spectrum of erythro β-phenylglyceric acid (fig-17). The infra-red spectra of these two compounds were recorded in major on Beckman IR 4 spectrophotometer.

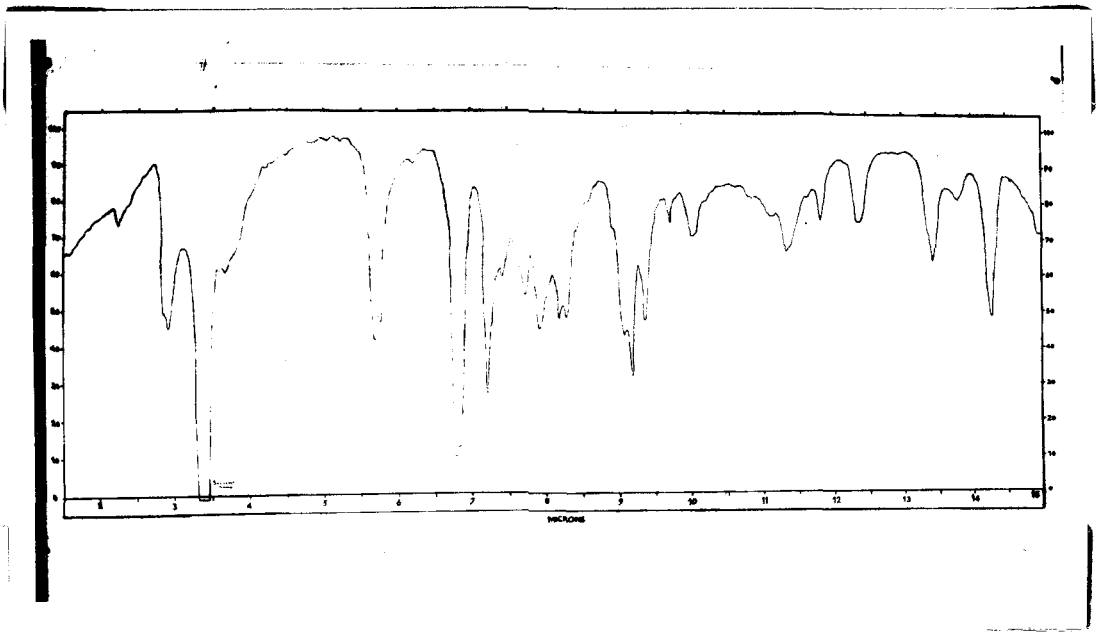


(Fig-15)

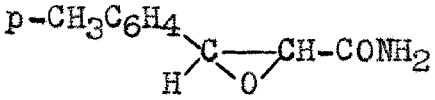
Hofmann reaction of 3-(p-toluyl)glycidamide (XCII) with bromine and alkali gave p-tolualdehyde (XCIII), p-toludine (XCIV) and p-toluylisocyanide (XCV) as the steam volatile products. p-Tolualdehyde was identified by preparation of 2:4-dinitrophenylhydrazone. The melting point and infra-red spectrum of 2:4-dinitrophenylhydrazone corresponded with the melting point and infra-red spectrum of 2:4-dinitrophenyl-hydrazone of p-tolualdehyde. p-Toludine was characterised by preparation of the benzoyl derivative. The melting point and



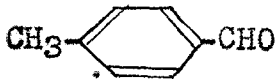
(Fig-16)



(Fig-17)



(XCII)

(XCIII) 

(XCIV) 

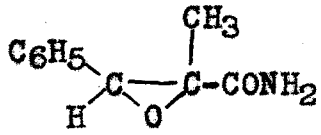
(XCV) 

(XCVI) 

(XCVII) 

infra-red spectrum of the benzoyl derivative corresponded with the melting point and infra-red spectrum of the benzoyl derivative of p-toludine. The steam distillate after the Hofmann reaction had the smell of isocyanide and by analogy with previous examples i.e. formation of phenylisocyanide and o-chlorophenylisocyanide in the Hofmann reaction of 3-phenylglycidamide and 3-(o-chlorophenyl)glycidamide respectively, the isocyanide obtained in the above reaction may be presumed to be p-toluylisocyanide. No non acid product was obtained from the residue left after steam distillation. Acidification of the residue gave p-toluic acid (XCVI) characterised by mixed melting point which was not depressed with authentic specimen and another acid which gave positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid[93]. The analysis of this acid agreed with the molecular formula of β-(p-toluyl)glyceric acid. On the basis of these tests and by analogy with formation of

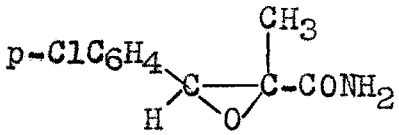
erythro β-phenylglyceric acid from the Hofmann reaction of 3-phenylglycidamide, this acid is characterised as erythro β-(p-toluyl)glyceric acid (XCVII).



(XCVIII)

2-Methyl-3-phenylglycidamide (XCVIII) when subjected to Hofmann reaction, gave on steam distillation benzaldehyde, aniline and phenylisocyanide as the steam volatile products. Benzaldehyde was characterised by conversion to 2;4-dinitrophenylhydrazone and mixed melting point which was not depressed with 2;4-dinitrophenylhydrazone of benzaldehyde. Aniline was identified by preparation of the benzoyl derivative and mixed melting point which was not depressed with benzanilide. Phenylisocyanide was characterised by infrared spectrum of the steam volatile products. The infra-red spectrum shows a band at 2250 cm^{-1} characterstic of isocyanide group[89,90]. The amount of isocyanide formed in the reaction was too little to be identified independently. However, by analogy with the formation of phenylisocyanide in the Hofmann reaction of 3-phenylglycidamide, the isocyanide obtained in the Hofmann reaction of 2-methyl-3-phenylglycidamide is characterised as phenylisocyanide. No non acid products were obtained from the

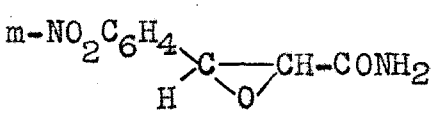
residue left after steam distillation. On acidification only benzoic acid identified by mixed melting point with authentic specimen, was isolated. The rest of the mass could not be crystallised.



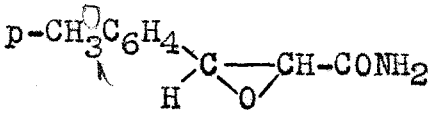
(XCIX)

Hofmann reaction of 2-methyl-3-(p-chlorophenyl)-glycidamide (XCIX) gave p-chlorobenzaldehyde and p-chloroaniline as the steam volatile products. p-Chlorobenzaldehyde was identified by preparation of the 2:4-dinitrophenylhydrazone and determination of mixed melting point which showed no depression with 2:4-dinitrophenylhydrazone of authentic specimen. p-Chloroaniline was identified by preparation of its benzoyl derivative and mixed melting point which was not depressed with benzoyl derivative of p-chloroaniline. As the infra-red spectrum of steam volatile reaction products was not recorded in this case, the presence of isocyanide could not be ascertained in the reaction products. No non acid product was isolated from the residue left after steam distillation. Acidification of the residue gave p-chlorobenzoic acid identified by mixed melting point which was not depressed with authentic specimen.

3-(m-Nitrophenyl)glycidamide (C) when subjected to Hofmann reaction with bromine and alkali, gave on steam distillation an aldehyde which could not be characterised as the quantity of the 2:4-dinitrophenylhydrazone formed by the aldehyde was very little. The residue left after steam distillation gave m-nitroaniline as the non acid product. m-Nitroaniline was identified by preparation of its benzoyl derivative and mixed melting point with the benzoyl derivative of authentic specimen (m-nitroaniline). The mixed melting point was not depressed. The analysis of the benzoyl derivative also agreed with the molecular formula of benzoyl derivative of m-nitroaniline. Acidification of the residue gave a gummy mass which could not be crystallised.



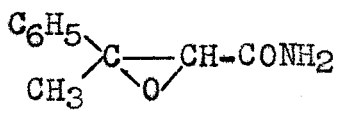
(C)



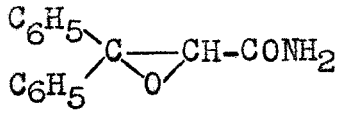
(CI)

Hofmann reaction of 3-(p-methoxyphenyl)glycidamide (CI) gave anisaldehyde as the only steam volatile product. Anisaldehyde was characterised by preparation of 2:4-dinitrophenylhydrazone and determination of mixed melting point which was not depressed with 2:4-dinitrophenylhydrazone of anisaldehyde. Ether extraction of the residue left after steam distillation gave a gummy mass which could not be

crystallised and which did not form benzoyl derivative. Acidification of the residue left after steam distillation gave anisic acid identified by mixed melting point which was not depressed with authentic specimen.



(CII)

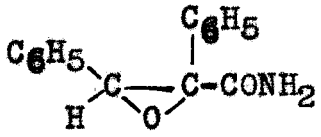


(CIII)

Hofmann reaction of 3-methyl-3-phenylglycidamide (CII) gave acetophenone as the steam volatile product. Acetophenone was identified by preparation of 2:4-dinitrophenylhydrazone and determination of mixed melting point with 2:4-dinitrophenylhydrazone of acetophenone. No depression was observed. Ether extraction of the residue left after steam distillation gave some starting glycidamide. Acidification of the residue gave a gummy mass which could not be crystallised.

Hofmann reaction of 3,3-diphenylglycidamide (CIII) gave only benzophenone as the steam volatile product. Benzophenone was identified by conversion to 2:4-nitrophenylhydrazone and determination of mixed melting point which was not depressed with 2:4-dinitrophenylhydrazone of authentic specimen. Prior to steam distillation, the reaction mixture during the heating stage of the reaction, had a clear but faint smell of isocyanide. However the smell was absent from the steam distillate and steam distillate did not form any dye

on hydrolysis with conc. hydrochloric acid, diazotisation and coupling with alkaline β-naphthol. From the residue left after steam distillation, a solid m.p. 240-50° was obtained but it could not be characterised as it could not be obtained in sufficiently pure form.

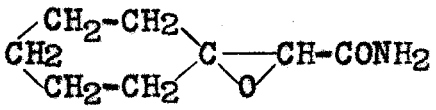


(CIV)

2,3-Diphenylglycidamide (CIV) when subjected to Hofmann reaction gave on steam distillation benzaldehyde characterised by conversion to 2;4-dinitrophenylhydrazone and determination of mixed melting point which was not depressed with 2;4-dinitrophenylhydrazone of authentic specimen. Ether extraction of the residue left after steam distillation gave very little viscous mass which could not be crystallised and which did not form any benzoyl derivative. Acidification of the residue gave a gummy mass from which only benzoic acid could be isolated and identified by mixed melting point which was not depressed with authentic specimen.

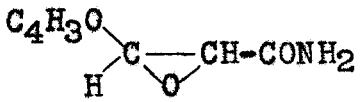
Hofmann reaction of 3,3-pentamethyleneglycidamide (CV) gave on steam distillation cyclohexanone. Cyclo hexanone was identified by preparation of the 2;4-dinitrophenylhydrazone and determination of the mixed melting point which was not depressed with the 2;4-dinitrophenylhydrazone of cyclo

hexanone . No non acid product was obtained from the residue left after steam distillation. Acidification of the residue gave a gummy mass which could not be crystallised.



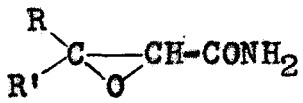
(CV)

Attempt was also made to prepare 3-furylglycidamide (CVI). However the crude glycidic ester decomposed during distillation. The ester is reported to be unstable[95].

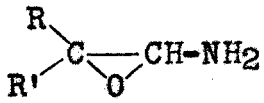


(CVI)

As has been described above, the Hofmann reaction of glycidamides (CVII) have shown that the corresponding amines (CVIII) or the hydroxy aldehydes (CIX) into which the glycidamines may decompose are not formed in the reaction. The



(CVII)



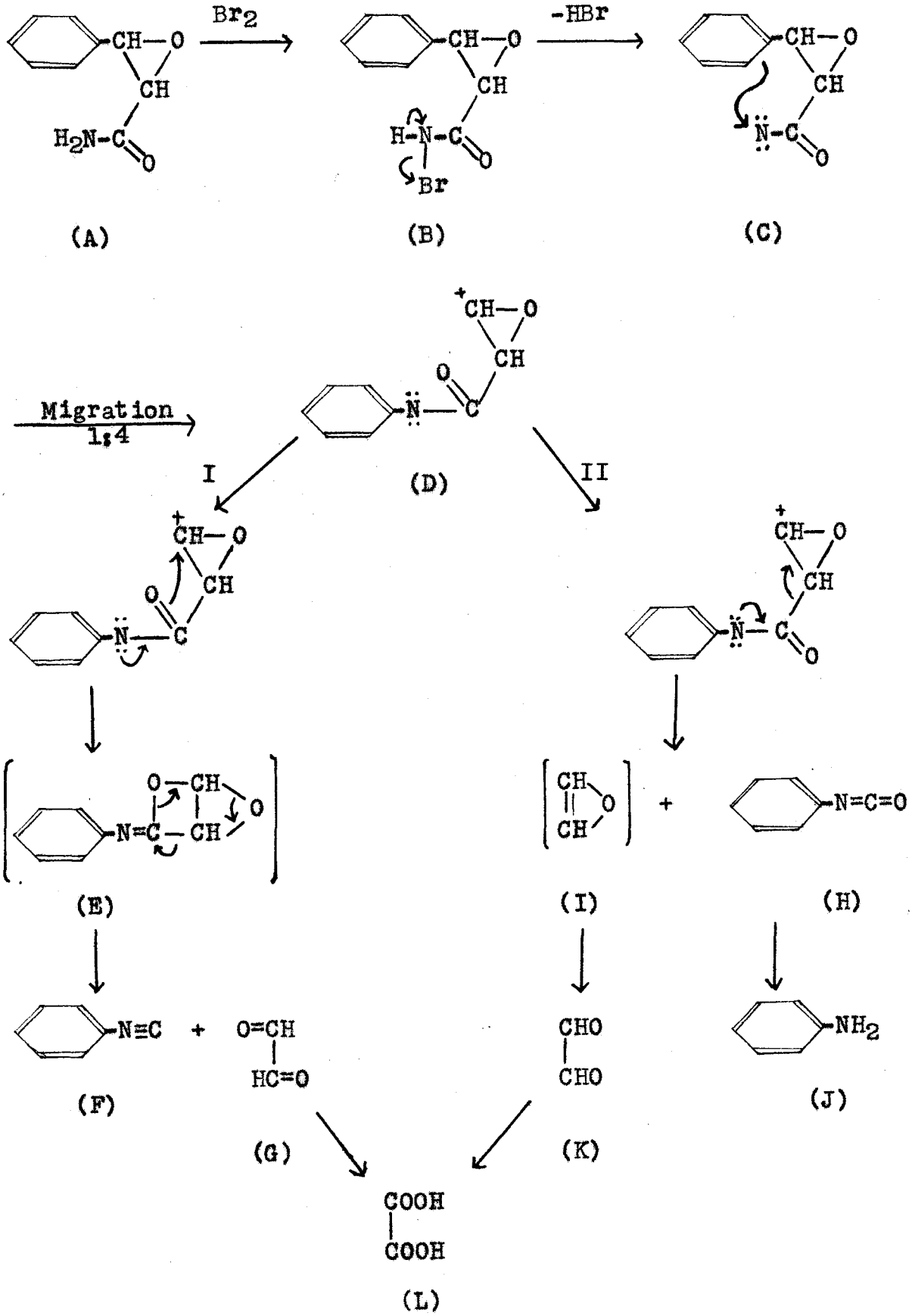
(CVIII)

(CIX)

products obtained are aldehydes or ketones, aromatic primary amines and isocyanides in very low yields. Isocyanides were not detected in all the cases studied. In one

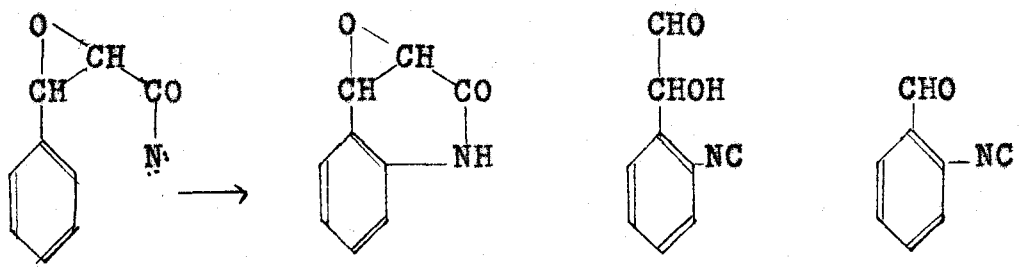
case, i.e. during the Hofmann reaction of 3,3-diphenylglycidamide a faint but clear smell of isocyanide was detected in the reaction mixture but the smell was absent from the steam distillate and further tests for the isocyanide failed. It is possible that in this case and in other cases where isocyanides were not detected, isocyanides might have been formed in very small amounts and as such these do not respond to the tests performed.

The following mechanism is proposed for the formation of isocyanides and aromatic primary amines in the Hofmann reaction of glycidamides. In the initial stages the reaction proceeds in the classical manner i.e. (A)→(B)→(C). At this stage (C), a 1:4 migration instead of the normal 1:2 migration of the phenyl group towards electrophile nitrogen leads to carbonium (D). The migration is facilitated by the neighbourhood of phenyl group and nitrogen atom in a quasi 5-membered ring system (C). Carbonium (D) can stabilise itself in two ways. In I carbonium (D) is converted to the cyclic intermediate (E) which because of its strained structure decomposes into isocyanide (F) and glyoxal (G). In II the carbonium (D) can stabilise itself by breaking into isocyanate (H) and acetylene oxide (I). Hydrolysis of (H) results in the formation of amine (J) (aniline in this case). Oxidation of (I) can result in the formation of glyoxal (K) or oxalic acid (L).


Br2
-HBr
(A)
(B)
(C)
Migration
1,4
I
II
(D)
(E)
(I)
(H)
(F)
(G)
(K)
(J)
(L)

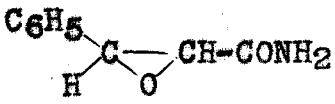
In the Hofmann reaction of 3-(o-chlorophenyl)-, 3-(m-chlorophenyl)-, 3-(p-chlorophenyl)- and 3-(p-toluyl)-glycidamides, primary aromatic amines are obtained in which the amino group is attached to the benzene ring at the point of attachment of the benzene ring to the epoxide ring in the starting glycidamide. This observation i.e. formation of o-chloroaniline, m-chloroaniline, p-chloroaniline and p-toludine in the Hofmann reaction of 3-(o-chlorophenyl)-, 3-(m-chlorophenyl)-, 3-(p-chlorophenyl)- and 3-(p-toluyl)-glycidamides respectively, supports the 1,4 migration suggested in the mechanism.

Had the isocyanide and the amine been formed by any other mechanism involving cyclic intermediates of the type (CX), the product would have been a compound having other groups along with the isocyanide group (CXI) & (CXII). Secondly the position of attachment of the isocyanide group and amino group would have been at a different place than the point of attachment of the benzene ring to the epoxide ring.

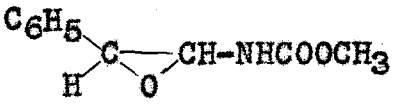


(CX) (CXI) (CXII)

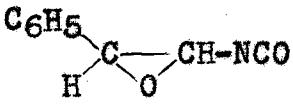
3-Phenylglycidamide (CXIII) failed to form the corresponding urethane (CXIV) when the Hofmann reaction was effected in sodium methoxide in methanol instead of aqueous alkali. The failure of formation of urethane lends additional support to the fact that glycidamides can not undergo the normal Hofmann reaction resulting in the formation of glycidamines or the urethanes and that the 1,4 migration takes place prior to the formation of isocyanate (CXV) the normal intermediate in the Hofmann reaction.



(CXIII)

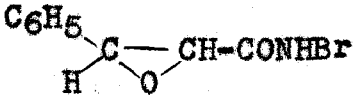


(CXIV)



(CXV)

Attempts were made to isolate the various intermediate involved. Of these only one i.e. 3-phenyl-N-bromoglycidamide (CXVI) could be isolated. However, this intermediate could not be obtained in pure state as it decomposed during crystallisation. The crude N-bromoglycidamide gave isocyanide on treatment with sodium hydroxide.



(XCVI)

The instability of the bromoamide may be the reason for the low yields of the isocyanide and amines that

are obtained in the Hofmann reaction of glycidamides. It is possible that prior to above rearrangement which results in the formation of isocyanide and amine, most of the bromoamide is decomposed and only a part of it undergoes the rearrangement.

Glyoxal or glycollic acid in which glyoxal is known to be converted under alkaline conditions by internal dismutation (modified cannizaro reaction[96]) were not isolated. In an attempt to isolate glycollic acid from the residue left after steam distillation in the Hofmann reaction of 3-phenylglycidamide, the residue was acidified and subjected to continuous ether extraction for 30 hours as glycollic acid is soluble in water. Glycollic acid was not obtained from the ether extract but β -phenylglyceric acid which is also soluble in water was obtained from it. β -Phenylglyceric acid gave positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid and gave oxalic acid on oxidation[93]. These tests were earlier performed with the residue as such without isolation of the acid and misled to think that these tests are due to glycollic acid as published in the note.

The presence of aromatic primary amines was detected after publication of the note and as such the note does not contain any reference to the formation of aromatic primary amines in the reaction products and to the mechanism of its formation.

Sodium hypobromite is known to be a strong oxidising agent and it is possible that the aldehydes or ketones that are obtained in the reaction, result from the oxidation of glycidamides or glycidic acids if the hydrolysis takes place before oxidation or of both. Except in the Hofmann reaction of 3-(m-nitrophenyl)glycidamide where the aldehyde that was formed in the reaction was not identified, in all other cases aldehydes and ketones obtained were the same from which the corresponding glycidic esters and then glycidamides were prepared.

Further oxidation of the aldehyde will account for the formation of acids isolated on acidification of the residue left after steam distillation. However, as the quantity of these acids was small, it is possible that other reactions like hydrolysis are also taking place along with oxidation. Glycidic acids resulting from hydrolysis may further be degraded to aldehydes and their derivatives (polymers) which may constitute the gummy masses obtained on acidification of the residue left after steam distillation and which could not be crystallised. The formation of ammonia during the reaction may be taken to be evidence of this hydrolysis.

Opening of the epoxide ring prior to (followed by hydrolysis) or after the above mentioned hydrolysis to glycidic acids will explain the formation of glyceric acids obtained in the reaction.

Attempts were made to increase the yield of isocyanide by performing the Hofmann reaction of 3-3-phenylglycidamide with (a) double the usual quantity of sodium hypobromite (b) heating the reaction mixture for longer time than the usual half an hour (c) using sodium hypochlorite instead of sodium hypobromite. HOwever no improvement in the yield of isocyanide was observed.

It was observed that some of the glycidamides which gave isocyanides, were not soluble in hypobromite solution. It was thought that the whole of glycidamide is not converted to N-bromoamide and hence the low yield of isocyanide. By adopting the procedure of ~~of~~ Hellerman[97] which was also used by Rahman and Farooq[7], use of excess of alakli (0.8 mole of alkali instead of usual 0.6 mole per mole of amide) in excess of water followed by stirring for one hour gave a clear solution of 3-phenylglycidamide in sodium hypobromite. However, this modification also did not improve the yield of isocyanide. or aniline.

NEW COMPOUNDS

The following new compounds were prepared for the first time during the course of present work:

1. Ethyl 3-(o-chlorophenyl)glycidate b.p. 144-5°/1-2 mm d_{20} 1.2364, n_D^{30} 1.5300
2. 3-(o-Chlorophenyl)glycidamide m.p. 180°
3. threo β-(o-Chlorophenyl)glyceric acid m.p. 207-8°
4. erythro β-(o-Chlorophenyl)glyceric acid m.p. 139°
5. 3-(m-Chlorophenyl)glycidamide m.p. 125-6°
6. erythro β-(m-Chlorophenyl)glyceric acid m.p. 118-20°
7. 3-(p-Chlorophenyl)glycidamide m.p. 176°
8. erythro β-(p-Chlorophenyl)glyceric acid m.p. 121-23°
9. α-Chloro-p-chlorocinnamide m.p. 184-5°
10. 3-(p-Toluyl)glycidamide m.p. 180-1°
11. erythro β-(p-Toluyl)glyceric acid m.p. 123-5°
12. 2-Methyl-3-(p-chlorophenyl)glycidamide m.p. 170°

...

EXPERIMETAL

EXPERIMENTAL

Preparation of Glycidic esters:

The glycidic esters were prepared by the general procedure of Darzen[66]. Sodium ethoxide and molecular sodium were used as condensing agents while benzene, toluene and ether were used as solvents. All the solvents were dried over anhydrous calcium chloride and sodium. Sodium ethoxide was prepared by dissolving sodium in dry absolute alcohol and completely removing the alcohol under suction with calcium chloride catches. All the liquid aldehydes were purified by distillation under reduced pressure under nitrogen atmosphere. Freshly distilled ethyl chloroacetate, ethyl α-bromopropionate and ethyl α-chlorophenylacetate were used. Molar ratio of aldehyde or ketone and α-haloester were used. Slight excess (1.1 mole) of sodium ethoxide was used. All the glycidic esters were tested for absence of halogens (chlorine) by beilsteins test except those glycidic esters which were prepared from chloroaldehydes, for the absence of unsaturation with bromine in carbontetrachloride and for the absence of keto group with ferric chloride.

Preparation of Glycidamides:

The glycidamides were prepared by the procedure of Fourneau[55] by the reaction of glycidic ester with aqueous

alcoholic ammonia. The reaction time varied with individual amides. In some cases, like 3-(m-nitrophenyl)glycidic ester the corresponding glycidamide precipitated almost immediately after passing ammonia into the solution of glycidic ester in aqueous-alcoholic ammonia while in other cases like ethyl 3,3-diphenylglycidate and ethyl 3,3-pentamethyleneglycidate, the reaction mixture has to be kept for three to four days for conversion of the glycidic ester to glycidamide. No attempt was made to find optimum conditions for the formation of glycidamides. The glycidamides were purified by crystallisation or repeated crystallisation where necessary. The residual products were not worked up. All the glycidamides which were prepared for the first time and the glycidamides whose melting point differed from the reported melting points were analysed.

Hofmann Reaction:

Hofmann reaction was performed according to the procedure described in the literature[4]. The Hofmann reaction was done using sodium hypobromite prepared by adding bromine (0.6 cc; 0.012 mole) to a solution of sodium hydroxide (2.4 g; 0.06 mole) in water (20 cc) at 0°. To the cold hypobromite solution, was added the finely divided dry glycidamide (0.01 mole) and the reaction mixture was stirred. The reaction mixture was warmed on a water bath for 40-45 minutes to a temperature of 60-70° and steam distilled.

Hofmann Reaction of 3-Phenylglycidamide

Preparation of Ethyl 3-phenylglycidate:

(a) By using sodium ethoxide:

Dry finely powdered sodium ethoxide prepared from sodium (6.25 g) and dry absolute alcohol (150 cc) was added little by little with stirring to a solution of benzaldehyde (26.5 g; 0.25 mole) and ethyl chloroacetate (30.6 g; 0.25 mole) in dry benzene (100 cc) taken in a three necked flask fitted with a reflux condenser and mechanical stirrer. The reaction flask was cooled with ice cold water during the addition of sodium ethoxide which was done in about two hours time. The reaction mixture was stirred for two hours at room temperature after addition of sodium ethoxide and then it was stirred for two hours at 70° on a water bath. The reaction mixture was cooled and poured in water and extracted with ether. The ether extract was dried over anhydrous calcium chloride overnight. Ether and benzene were distilled off in a claisen flask under reduced pressure using water pump and the residue was distilled in a flask with built in condenser and column. Ethyl 3-phenylglycidate was obtained b.p. 122-4°/2 mm (reported[98] 96°/1 mm and 142-5°/8 mm) Yield 34 g.

(b) By using molecular sodium:

A mixture of benzaldehyde (53 g) and ethyl

chloroacetate (61.2 g) was added slowly with stirring over a period of four hours to cooled dry toluene (200 cc) containing molecular sodium (12 g) in suspension, taken in a three necked flask fitted with a dropping funnel, stirrer, alcohol thermometer and calcium chloride tube. The reaction flask was cooled by ice-salt mixture. The rate of addition of mixture of benzaldehyde and ethyl chloroacetate was so adjusted that the inside temperature of the flask did not exceed 5^{o}. After the end of the reaction, alcohol was added to destroy any unreacted sodium. The reaction mixture was poured in water and extracted with ether. The glycidic ester was distilled as before. Yield 60 g.

Preparation of 3-Phenylglycidamide:

Gaseous ammonia was passed into a mixture of ethyl 3-phenylglycidate (25 g), liquor ammonia (125 cc) and alcohol (250 cc) for one hour. The reaction mixture was kept for two hours. Alcohol was removed under suction and the precipitated amide was filtered. Crystallisation from methanol gave plates m.p. 148^{o} (reported[55] 148^{o}). Yield 12 g.

Hofmann Reaction of 3-Phenylglycidamide :

Finely powdered dry 3-phenylglycidamide (2.45 g; 0.015 mole) was added to a cold solution of sodium hypobromite, prepared by adding bromine (0.9 cc; 0.018 mole) to a solution

of sodium hydroxide (3.6 g: 0.09 mole) in water (30 cc), at 0°. On stirring for 10-15 minutes the whole mass became semi-solid and further stirring became impossible. The reaction mixture was left for fifteen minutes and then heated to 60-65° for 45 minutes on a water bath. The semi solid mass went into solution and the solution turned reddish brown. After about 20 minutes smell of isocyanide appeared and a solid (sodium salt) precipitated out. The evolved gases when passed in Nesslers reagent turned it brown. The reaction mixture was distilled with steam. The sodium salt dissolved during steam distiliation. The steam distillate had the smell of isocyanide.

A portion of the steam distillate was acidified with hydrochloric acid and sodium nitrite solution was added to it in cold. Alkaline β-naphthol solution was added to the cold solution. A brilliant orange dye was obtained.

The remaining steam distillate was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. Infra-red spectrum of a portion ofthe residue left after removal of ether was recorded. The infra-red spectrum (fig-12.) shows absorption at 2225 cm^{-1} (cf. isocyanide[89,90]), 1700 cm^{-1} (cf. aromatic aldehyde[99]) and 3400 & 3500 cm^{-1} (cf. aromatic amines[100]).

Steam Volatile Portion

(a) Carbonyl Component:

A portion of the ether extract was dried over

sodium sulphate. The residue obtained on removal of ether was treated with 2;4-dinitrophenylhydrazine reagent. It formed a 2;4-dinitrophenylhydrazone m.p. 236-7°. Mixed melting point with 2;4-dinitrophenylhydrazone of benzaldehyde was not depressed. Another portion of the residue obtained on evaporation of ether was treated with phenylhydrazine reagent. It formed a phenylhydrazone m.p. 155-6°(alcohol). Mixed melting point with phenylhydrazone of benzaldehyde was not depressed. The infra-red spectrum of 2;4-dinitrophenylhydrazone was also identical with infra-red spectrum of 2;4-dinitrophenylhydrazone of benzaldehyde.

Analysis;

	C	H	N
(a) 2;4-dinitrophenylhydrazone			
Cal. for $C_{13}H_{10}N_4O_4$	54.55	3.49	19.5
Found	53.87	3.70	18.92
	.68	.21	.6
(b) Phenylhydrazone			
Cal. for $C_{13}H_{12}N_2$	79.5	6.1	14.27
Found	79.79	6.3	13.8
	.3	.2	.5

(b) Non Carbonyl Component;

Another portion of the ether extract was dried over anhydrous sodium sulphate. Evaporation of the ether gave 0.1 cc of a liquid to which benzoyl chloride (0.5 cc) and 10 % sodium hydroxide (20 cc) were added and the mixture was shaken for 20 minutes. A solid separated which was filtered, washed

with sodium hydroxide solution and water. Crystallisation of the benzoyl derivative from benzene-petrol gave needles m.p. 162°. Mixed melting point with benzanilide was not depressed. The infra-red spectrum of the benzoyl derivative was also identical with the infra-red spectrum of benzanilide.

Analysis:

	C	H	N
Cal. for $C_{13}H_{11}NO$	79.16	5.62	7.1
Found	79.98	5.40	7.12

(c) Water Soluble Component:

The aqueous layer left after ether extraction of the steam distillate was acidified and treated with 2:4-dinitrophenylhydrazine reagent. 2:4-dinitrophenylhydrazone was not obtained.

Hofmann reaction was repeated with 22.45 g 3-phenylglycidamide. The steam distillate obtained in the reaction was extracted with ether and the ether extract was washed with 4% hydrochloric acid[101]. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. The residue was acidified with conc. hydrochloric acid and warmed on a water bath for 5 minutes. Water (20 cc) was added to the residue and it was again extracted with ether. The aqueous layer was made alkaline with sodium hydroxide solution

and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. The residue (one drop) was treated with benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution (20 cc). On shaking for twenty minutes benzoyl derivative was obtained. Crystallisation from benzene-petrol gave needles m.p. 162°$_{\lambda}^{(5-9)}$ Mixed melting point with benzanilide was undepressed.

In a separate experiment, starting from 4.89 g of 3-phenylglycidamide 150 mg of 2:4-dinitrophenylhydrazone of benzaldehyde and 120 mg of benzanilide were obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried and ether was distilled off. No residue was obtained.

(b) Acid Component:

The aqueous layer left after ether extraction of the non acid component was acidified with hydrochloric acid and extracted with ether. Ether extract was dried over anhydrous sodium sulphate and ether was distilled off. The residue was crystallised from benzene-petrol repeatedly. An acid m.p. 121° (0.6 g) was obtained. Mixed melting point with benzoic acid was undepressed. The mother liquor gave a brown gummy mass (which turns green on keeping for some days) which could not be

crystallised. The gummy mass was heated to 200°(to effect decarboxylation) in a distilling flask fitted with a condenser. The receiver contained 2:4-dinitrophenylhydrazine reagent. However, there was practically no distillate and 2:4-dinitrophenylhydrazone was not obtained. Chromatography of the gummy residue on acid alumina using benzene, benzene-petrol and methanol as eluants, resulted in much adsorption and only benzoic acid was obtained from the various fractions in small amounts.

The aqueous layer left after extraction of the acid portion was subjected to continuous ether extraction for 30 hours. The ether extract was dried and ether was distilled off. Crystallisation of the residue from methanol-benzene gave an acid m.p. 121-2°. The acid was soluble in water and gave negative test for nitrogen. The acid was warmed with conc. sulphuric acid and to the cooled solution 2 drops of 5% alcoholic guaiacol solution was added. A red-violet colour was obtained (cf. test of hydroxy acids[93]).

Analysis:	C	H
Cal. for $C_9H_{10}O_4$	59.33	5.53
Found	60.16	5.77

Preparation of the methyl ester of the hydroxy acid:

An ethereal solution of the isolated hydroxy acid was treated with excess of ethereal solution of diazomethane and kept overnight. The excess ether and diazomethane were

evaporated off. Crystallisation of the residue from benzene-petrol gave a product m.p. 87° (Cf. methyl ester of β-phenylglyceric acid m.p. 87° [91]).

Preparation of benzoyl derivative of the hydroxy acid:

The isolated hydroxy acid (300 mg) was dissolved in pyridine (3 cc) and benzoyl chloride (0.5 g) was added to it. The reaction mixture was left overnight, acidified with hydrochloric acid and poured in cold water. The precipitated benzoyl derivative was filtered. Crystallisation of the benzoyl derivative from benzene gave crystal melting at 187-8° (cf. dibenzoyl derivative of β-phenylglyceric acid m.p. 187° [91]).

Acid hydrolysis of ethyl 3-phenylglycidate:

Ethyl 3-phenylglycidate (1 g) was suspended in water which has been acidified with conc. hydrochloric acid. The suspension was heated with occasional shaking for 3-4 hours. As no solid separated on cooling, the liquid in the flask was neutralised with aqueous sodium carbonate solution and then excess of sodium carbonate solution was added. The reaction mixture was refluxed for 3 hours with frequent shaking. The reaction mixture was cooled and extracted with ether (to remove any unhydrolysed ester). The aqueous layer was acidified and extracted with ether (excess). The ether

extract was dried over anhydrous sodium sulphate and ether was distilled off. Crystallisation of the residue from benzene-methanol gave an acid m.p. 141° (cf. threo β-phenylglyceric acid m.p. 141° [90,91,125]).

Oxidation of the hydroxy acid m.p. 121-2°:

The hydroxy acid m.p. 121-2° (0.5 g) was added to a flask containing aqueous sodium carbonate solution (25 cc; 10%). Potassium permanganate solution was added to the mixture and the flask was heated on a water bath. Addition of the permangante solution was continued till decolourisation of the permanganate stopped. The solution was cooled and filtered. The filtrate was extracted with ether and the aqueous layer was divided in two parts. Ether extract when worked up gave benzaldehyde identified by mixed melting point of the 2:4-dinitrophenyl-hydrazone with that of authentic specimen. One portion of the filtrate was taken and acidified with Hcl. The precipitated acid was crystallised from hot water. An acid m.p. 121° was obtained. Mixed melting point with benzoic acid was undepressed. The other portion of the filtrate was acidified with acetic acid and calcium chloride solution was added to it. A white precipitate was obtained. The precipitate was insoluble in acetic acid but soluble in hydrochloric acid. The precipitate decolourised warm acidified potassium permanganate solution.

Hofmann reaction of 3-Phenylglycidamide under special conditions:

Hofmann reaction was performed under special conditions using sodium methoxide and bromine in methanol. 3-Phenylglycidamide (5.34 g) was dissolved in methanol (40 cc) and the solution was mixed with a solution of sodium (1.54 g) in methanol (30 cc). Bromine (1.8 cc) was added with stirring to the cold solution of glycidamide and sodium methoxide. The resulting solution was heated on a water bath for 40 minutes to 60-70°. The reaction mixture was cooled and acidified with acetic acid (pH 6). The methanol was removed under suction. The residue was washed with water to remove sodium bromide and extracted with ether. As the solid which was obtained on evaporation of methanol, was found to be insoluble in ether and water it was separated by filtration. Ether extract was dried over anhydrous sodium sulphate and the ether was distilled off. Crystallisation of the residue from methanol gave plates m.p. 148°. Mixed melting point with 3-phenylglycidamide was undepressed. The rest of the gummy mass obtained from the mother liquor, could not be crystallised. The solid which separated during ether extraction (which did not dissolve in ether) was also found to be 3-phenylglycidamide. In all about 3.4 g 3-phenylglycidamide was recovered.

Hofmann reaction of 3-phenylglycidamide with sodium hypochlorite:

Hofmann reaction was done using sodium hypochlorite instead of sodium hypobromite. A 0.5 N solution of sodium hypochlorite was prepared by adding conc. hydrochloric acid (42 g) through a dropping funnel to potassium permanganate (33 g) taken in a flask fitted with a delivery tube. The generated chlorine was passed in 10 % sodium hydroxide solution (100 cc) cooled in ice bath.

3-Phenylglycidamide (1.63 g; 0.01 mole) was added to cold sodium hypochlorite solution (40 cc) and the mixture was stirred. The amide did not go in solution nor did it formed a semisolid mass as in the case of Hofmann reaction with sodium hypobromite. The resulting mixture was heated on a wtaer bath to 60-65° for 40 minutes. On heating the amide dissolved completely in the hypochlorite solution and then turbidity appeared. The reaction mixture was steam distilled. The steam distillate had faint smell of isocyanide Steam distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulphate. Ether was distilled off and the residue was divided in two parts. To one part 2:4-dinitrophenylhydrazine reagent was added. 30 mg 2:4-dinitrophenylhydrazone of benzaldehyde was obtained. To the other portion of the residue, benzoyl chloride (0.5 cc) and 10% sodium hydroxide (20 cc) were added and the reaction

mixture was shaken for 30 minutes. The crude benzoyl derivative was filtered. Crystallisation from benzene-petrol gave 20 mg benzoyl derivative m.p. 162. Mixed melting point with benzanilide did not show any depression.

Hofmann reaction with excess of sodium hypobromite:

Hofmann reaction of 3-phenylglycidamide was repeated with double the quantity of sodium hypobromite i.e. 0.024 mole of bromine and 0.12 mole of sodium hydroxide instead of usual 0.012 mole of bromine and 0.06 mole of sodium hydroxide per 0.01 mole of the amide. However, no improvement in the yield was observed as the smell of the isocyanide was faint and the amount of 2:4-dinitrophenyl-hydrazone of benzaldehyde and benzanilide obtained after the reaction were practcally the same as were obtained when the Hofmann reaction was done with usual quantity of sodium hypobromite.

Hofmann reaction with longer heating time:

Hofmann reaction of 3-phenylglycidamide was repeated by heating the reaction mixture obtained by adding amide to hypobromite solution, to 60-65° for 1½ hours instead of usual 40 minutes. Here again no improvement in the yields of isocyanide, benzaldehyde (in the form of 2:4-dinitrophenyl-hydrazone) and aniline (in the form of benzanilide) was noticed.

Preparation of 3-phenyl-N-bromoglycidamide:

3-Phenyl-N-bromoglycidamide was prepared by the method of Houser & Renfraw[102]. 3-Phenylglycidamide (2.45 g; 0.015 mole) was added to cold solution of sodium hypobromite prepared from bromine (0.9 cc; 0.018 mole) and sodium hydroxide (4.8 g; 0.12 mole) in water (60 cc). Excess of sodium hydroxide was used in order to obtain solution of the glycidamide in hypobromite[7,97]. The reaction mixture was stirred for two hours. A clear solution was obtained. The solution was filtered into 20 cc 1:1 acetic acid (10 cc acetic acid and 10 cc water). The precipitated N-bromoamide was filtered, washed with water and dried. Crystallisation was attempted with methanol, benzene, chloroform and acetic acid-water. All the solvents turned brown (probably due to liberation of bromine). With acetic acid-water an impure product m.p. 120-26° (d) was obtained.

Reaction of 3-phenyl-N-bromoglycidamide with sodium hydroxide:

The crude N-bromoamide obtained above was added to a solution of 3.6 g of sodium hydroxide in water (30 cc) and the reaction mixture was heated on a water bath to 60-65° for 40 minutes. The N-bromoamide went into solution and after half an hour smell of ammonia and faint smell of isocyanide was detected.

Hofmann Reaction of 3-(o-Chlorophenyl)glycidamide

Preparation of Ethyl 3-(o-chlorophenyl)glycidate:

Ethyl 3-(o-chlorophenyl)glycidate was prepared by Darzen's method according to the procedure described by Martynov & Olman[63,64] for the preparation of ethyl 3-phenylglycidate and ethyl 3-(p-chlorophenyl)glycidate. A mixture of o-chlorobenzaldehyde (35.1 g; 0.25 mole) ethyl chloroacetate (30.6 g; 0.25 mole) and dry absolute ether (300 cc) was taken in a three necked flask fitted with a dropping funnel, mechanical stirrer, alcohol thermometer and calcium chloride tube. Freshly prepared sodium ethoxide (18.7 g; 0.275 mole) was added little by little with stirring in three hours to the reaction mixture. The temperature was maintained at -5 to 5° for four hours followed by two hours stirring at room temperature. The reaction mixture was left overnight. The reaction mixture was poured in water and extracted with ether. The ether extract was washed with water four times and the ether extract was dried over anhydrous calcium chloride overnight. Major portion of ether was distilled off in a claisen flask and distillation of the residue under reduced pressure in a flask fitted with a built in condenser and column gave ethyl 3-(o-chlorophenyl)glycidate b.p. 144-5° /1-2 mm, d_{20} 1.2364; n_D^{30} 1.5300. Yield 30g.

The infra-red spectrum of the glycidic ester shows

two bands in the carbonyl stretching region (1700-1800cm^{-1}). The glycidic ester did not give any colour with ferric chloride solution.

Preparation of 3-(o-Chlorophenyl)glycidamide:

Gaseous ammonia was passed into a mixture of ethyl 3-(o-chlorophenyl)glycidate (20 g), liquor ammonia (100 cc) and ethyl alcohol (200 cc) for half an hour. The crystals of amide started separating after fifteen minutes. The reaction mixture was kept for two hours. Alcohol was removed under suction and the crude amide filtered. Crystallisation from methanol gave needles m.p. 180°. Yield 13.5 g.

Analysis:

		C	H	N	Cl
Cal. for $C_9H_8O_2NCl$		54.68	4.05	7.09	17.9
Found	(i)	54.86	4.31	7.19	17.69
	(ii)	54.70	4.07	7.23	17.40

Hofmann Reaction of 3-(o-Chlorophenyl)glycidamide:

Dry finely powdered 3-(o-chlorophenyl)glycidamide (1.97 g) was added with stirring to a cooled solution of sodium hypobromite, prepared from sodium hydroxide (2.4 g) in water (20 cc) and bromine (0.6 cc), at 0°. After twenty minutes stirring practically all glycidamide went into solution. The reaction mixture was heated on a water bath to a temperature

of 60-65° for 45 minutes. After about half an hour, the clear solution became turbid and a solid (sodium salt) separated. The reaction mixture had the smell of ammonia and faint smell of isocyanide. The reaction mixture was distilled with steam. The steam distillate was extracted with ether.

The ether extract was dried over anhydrous sodium sulphate. The ether was distilled off from a portion of ether extract. The infra-red spectrum (fig-13) of the residue shows absorption at 2250 cm^{-1} (cf. isocyanide[89,90]), 1700 cm^{-1}(cf. aromatic aldehyde[99]) and 3400 & 3500 cm^{-1} (cf. aromatic amine [100]).

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from another portion of the dried ether extract of the steam distillate. The residue was treated with 2:4-dinitrophenylhydrazine reagent. 2:4-dinitrophenylhydrazone m.p. 207-8° (benzene-petrol) was obtained. Mixed melting point with 2:4-dinitrophenylhydrazone of o-chlorobenzaldehyde was undepressed.

In a separate experiment, starting from 1.97 g of 3-(o-chlorophenyl)glycidamide, 30 mg of 2:4-dinitrophenylhydrazone of o-chlorobenzaldehyde was obtained.

(b) Non Carbonyl Component:

Ether was distilled off from another portion of

dried ether extract of the steam distillate. To the residue benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution (20 cc) were added and the reaction mixture was shaken for half an hour. The benzoyl derivative was filtered, washed with sodium hydroxide solution and water. Crystallisation from benzene-petrol gave needles m.p. 98-99°. Mixed melting point with benzoyl derivative of o-chloroaniline did not show any depression.

In a separate experiment starting from 1.97 g 3-(o-chlorophenyl)glycidamide, 40 mg of benzoyl derivative of o-chloroaniline was obtained.

(c) Water Soluble Component:

The aqueous layer left after ether extraction of the steam distillate was acidified and treated with 2:4-dinitrophenylhydrazine reagent. 2:4-dinitrophenylhydrazone was not obtained.

Hofmann reaction was repeated with 13.65 g 3-(o-chlorophenyl)glycidamide. The steam distillate obtained in the reaction was washed with 4% hydrochloric acid and extracted with ether. The ether extract was dried and ether was distilled off. The residue was acidified with conc. hydrochloric acid and warmed on a water bath for five minutes. Water (15 cc) was added to the acidified residue and it was extracted with ether. The aqueous layer was made alkaline with sodium hydroxide solution

and extracted with ether. The ether extract was dried and ether was distilled off. No residue was obtained showing that the isocyanide is formed in traces only.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. No residue was obtained.

(b) Acid Component:

The aqueous layer left after ether extraction of non acid component was acidified and extracted with ether. Ether extract was dried over anhydrous sodium sulphate and ether was distilled off. Repeated crystallisation of the residue from benzene-petrol gave an acid m.p. 141° (15 mg). Mixed melting point with o-chlorobenzoic acid was not depressed. From the mother liquor, another acid (0.9 g) was obtained by repeated crystallisation from benzene-methanol. The acid melted at 139° and was soluble in water. A pinch of the acid was warmed with conc. sulphuric acid (2 cc) and to the cooled solution 2 drops of 5% alcoholic guaiacol solution was added. A deep red-violet colour developed. The acid showed

negative test for nitrogen. Mixed melting point with the acid obtained by alkaline hydrolysis of ethyl 3-(o-chlorophenyl)-glycidate was undepressed.

Analysis:

	C	H	Cl
Cal. for $C_9H_9O_4Cl$	49.7	4.16	16.38
Found	50.0	4.32	16.3

Alkaline Hydrolysis of Ethyl 3-(o-chlorophenyl)glycidate:

The glycidic ester was hydrolysed by the method of English & Heywood[94]. Ethyl 3-(o-chlorophenyl)glycidate (1 g) was mixed with 10% sodium hydroxide (30 cc) and the mixture was left overnight. The reaction mixture was refluxed gently for 12 hours. After cooling the reaction mixture was extracted with ether to remove unhydrolysed ester. The aqueous layer was acidified with hydrochloric acid and extracted with excess of ether. Ether extract was dried over anhydrous sodium sulphate and ether was distilled off. The residue on crystallisation from benzene-petrol gave an acid m.p. 139° (0.6 g). The acid gave positive colour test with guaiacol and conc. H_2SO_4.

Acid Hydrolysis of Ethyl 3-(o-chlorophenyl)glycidate:

The acid hydrolysis was done according to the procedure of Blicke & Faust[65]. Ethyl 3-(o-chlorophenyl)-glycidate (2 g) was suspended in 1% hydrochloric acid (50 cc)

and the mixture was refluxed for four hours. After refluxing no solid separated. The mixture was basified with sodium carbonate solution and the reaction mixture was again refluxed for four hours. The reaction mixture was cooled and extracted with ether. The aqueous layer was acidified and extracted with excess of ether. Ether extract was dried over anhydrous sodium sulphate and the ether was distilled off. Crystallisation of the residue from benzene-methanol gave an acid m.p. 207-8° (1.2g). A pinch of acid was warmed with conc. sulphuric acid (2 cc) and to the cooled solution 2 drops of 5% alcoholic solution of guaiacol was added. A red-violet colour was obtained.

Analysis:

	C	H	Cl
Cal. for $C_9H_9O_4Cl$	49.7	4.16	16.38
Found	49.33	4.27	16.2

Alkaline Hydrolysis of 3-(o-chlorophenyl)glycidamide:

3-(o-Chlorophenyl)glycidamide was hydrolysed in a manner similar to that described for the alkaline hydrolysis of ethyl 3-(o-chlorophenyl)glycidate. After hydrolysis an acid m.p. 207-8° (benzene-methanol) was obtained. Mixed melting point with the acid obtained by the acid hydrolysis of ethyl 3-(o-chlorophenyl)glycidate was undepressed.

Hofmann Reaction of 3-(m-Chlorophenyl)glycidamide

Preparation of Ethyl 3-(m-chlorophenyl)glycidate:

m-Chlorobenzaldehyde (23.4 g; 0.167 mole) and ethyl chloroacetate (20.4 g; 0.167 mole) were condensed together in presence of sodium ethoxide as condensing agent and dry ether as solvent. The reaction was done at -5 to 5°. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)glycidate. Distillation gave ethyl 3-(m-chlorophenyl)glycidate b.p. 140-2°/1-2 mm; d_{20} 1.2498 n_D^{30} 1.5340 (reported[103] 150-5°/5 mm; n_D^{20} 1.5357). Yield 22 g.

Infra-red spectrum in chloroform (fig-2) shows a single band at 1750 cm^{-1} instead of two bands characterstic of glycidic esters at 1737 & 1753 cm^{-1}. N.M.R. spectrum was also recorded (fig-5).

Preparation of 3-(m-Chlorophenyl)glycidamide:

Ethyl 3-(m-chlorophenyl)glycidate (15 g) was dissolved in alcohol (150 cc) and to the solution liquor ammonia (75 cc) was added. Gaseous ammonia was passed in the reaction mixture for 45 minutes and the reaction mixture was kept for one hour. Alcohol was removed under suction and the crude amide separated by filtration. Crystallisation from methanol gave plates m.p. 125-6°. Yield 6.5 g.

Analysis:

	C	H	N	Cl
Cal. for $C_9H_8O_2NCl$	54.68	4.05	7.09	17.9
Found	55.04	4.17	6.91	17.8

Hofmann Reaction of 3-(m-Chlorophenyl)glycidamide:

Finely powdered dry 3-(m-chlorophenyl)glycidamide (1.97 g) was added with stirring to a cooled solution of sodium hypobromite, prepared from bromine (0.6 cc) and sodium hydroxide (2.4 g) dissolved in water (20 cc), at 0°. After stirring for fifteen minutes, the whole mass became semi-solid and further stirring became impossible. The reaction mixture was heated on a water bath to 60-65° for 40-45 minutes. After 30 minutes heating, the reaction mixture became a homogeneous pale yellow solution and faint smell of isocyanide was detected. On cooling for 10-15 minutes a solid precipitated out which went into solution during steam distillation. The reaction mixture was distilled with steam. The steam distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulphate.

Ether was distilled off from a portion of the ether extract and infra-red spectrum of the residue was recorded. The infra-red spectrum (fig-14) shows absorption at 2250 cm^{-1} (cf. isocyanide[89,90]), 1700 cm^{-1} (cf. aromatic aldehyde[99]) and 3400 & 3500 cm^{-1} (cf. aromatic amine[100]).

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from a portion of the dried ether extract of the steam distillate. To the residue 2:4-dinitrophenylhydrazine reagent was added. Crystallisation from benzene-petrol gave 2:4-dinitrophenylhydrazone m.p. 247-8°. Mixed melting point with 2:4-dinitrophenylhydrazone of m-chlorobenzaldehyde was undepressed.

(b) Non Carbonyl Component:

To the residue obtained on evaporation of the ether from the other portion of the ether extract of the steam distillate, benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution (25 cc) were added and the reaction mixture was shaken for 30 minutes. The benzoyl derivative was filtered, washed with sodium hydroxide solution and water. Crystallisation from benzene gave needles m.p. 120-2°. Mixed melting point with benzoyl derivative of m-chloroaniline was undepressed.

Starting from 1.97 g 3-(m-chlorophenyl)glycidamide 20 mg 2:4-dinitrophenylhydrazone of m-chlorobenzaldehyde and 25 mg of benzoyl derivative of m-chloroaniline were obtained.

(c) Water Soluble Component:

The aqueous layer left after ether extraction of steam distillate was acidified and treated with

2:4-dinitrophenylhydrazine reagent. 2:4-dinitrophenylhydrazone was not obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. No residue was obtained.

(b) Acid Component:

The aqueous layer left after extraction of the non acid component was acidified with hydrochloric acid and extracted with ether. Ether extract was dried over anhydrous sodium sulphate and ether was distilled off. Repeated crystallisation of the residue from benzene-methanol gave an acid m.p. 118-20° (0.45 g). The acid was soluble in water and gave negative test for nitrogen. A pinch of the acid was warmed with conc. sulphuric acid (2 cc) and to the cooled solution 2 drops of 5% alcoholic solution of guaiacol were added. A red violet colour was obtained. Mixed melting point with the acid obtained by alkaline hydrolysis of ethyl 3-(m-chlorophenyl)glycidate was undepressed.

Alkaline Hydrolysis of Ethyl 3-(m-chlorophenyl)glycidate:

Ethyl 3-(m-chlorophenyl)glycidate (1 g) was mixed with 10% sodium hydroxide solution (30 cc) and the reaction mixture was left overnight. The reaction mixture was refluxed gently for 12 hours. The reaction mixture was cooled and extracted with ether to remove unhydrolysed ester. The aqueous layer was acidified with hydrochloric acid and extracted with excess of ether. The ether extract was dried over anhydrous sodium sulphate and ether was removed by distillation. Crystallisation of the residue from benzene-methanol gave an acid m.p. 118-9° (0.55 g). The acid gave positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid.

Hofmann Reaction of 3-(p-Chlorophenyl)glycidamide

Preparation of Ethyl 3-(p-chlorophenyl)glycidate:

(a) By using sodium ethoxide:

p-Chlorobenzaldehyde (35.1 g) and ethyl chloroacetate (30.6 g) were condensed together in the presence of sodium ethoxide (18.7 g) and dry ether (300 cc) as solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)glycidate. Distillation gave ethyl 3-(p-chlorophenyl)glycidate b.p. 147°/1 mm (reported[66,64] 155-60°/3-4 mm & 160°/1 mm) Yield 33 g.

(b) By using molecular sodium:

A mixture of p-chlorobenzaldehyde (35.1 g) and ethyl chloroacetate (30.6 g) was added slowly with stirring over a period of four hours to cooled dry toluene (150 cc) containing molecular sodium in suspension (6 g), taken in a three necked flask fitted with a dropping funnel, stirrer, alcohol thermometer and calcium chloride tube. The rate of addition of mixture of p-chlorobenzaldehyde and ethyl chloroacetate was so adjusted that the inside temperature of the flask did not exceed 5°. After the end of reaction alcohol was added to destroy any unreacted sodium and the reaction mixture was poured in water and extracted with ether. The glycidic ester was distilled as before. The glycidic ester

distilled at 147-8°/1 mm. Yield 34.5 g.

Infra-red spectrum in chloroform (fig-3) of ethyl 3-(p-chlorophenyl)glycidate shows a single band at 1750 cm^{-1} instead of two bands at 1737 and 1753 cm^{-1}. N.M.R. spectrum (fig-6) was also recorded.

Alcoholic solution of the glycidic ester gave no colour with 1% alcoholic ferric chloride solution.

Preparation of 3-(p-Chlorophenyl)glycidamide:

(a) Ethyl 3-(p-chlorophenyl)glycidate (20 g) was dissolved in alcohol (200 cc) and to the solution liquor ammonia (100 cc) was added. Ammonia gas was passed in the solution for one hour. The reaction mixture was left for two hours and the alcohol was removed under suction. The precipitated amide was filtered and crystallised from methanol. Two fractions, one melting at 176° (7 g) and the other melting at 184-5° (1.2 g) were obtained. The two amides were analysed. The analysis of the amide m.p. 176° agreed with the molecular formula of glycidamide. The analysis of amide m.p. 184-5° was found to agree with the molecular formula of α-chloro- p-chlorocinnamide ($p\text{-}ClC_6H_4\text{-}CH{=}CClCONH_2$). α-Chloro-α-β-unsaturated esters are known to be produced as side reaction products in the Darzens glycidic ester condensation[66].

Analysis:

		C	H	N	Cl
I	Amide m.p. 176°				
	Cal. for $C_9H_8NO_2Cl$	54.68	4.05	7.09	17.9
	Found	54.67	4.15	6.71	17.4
II	Amide m.p. 184-5°				
	Cal. for $C_9H_7NOCl_2$	50.00	3.24	6.48	32.81
	Found	50.01	3.38	6.34	32.60

(b) 3-(p-Chlorophenyl)glycidamide was prepared again using ethyl 3-(p-chlorophenyl)glycidate prepared by the method using molecular sodium as the condensing agent by the same procedure as has been described above. Reaction with ammonia gave only one amide m.p. 176° (methanol). Mixed melting point with the amide m.p. 176° obtained by the reaction of ammonia on ethyl 3-(p-chlorophenyl)glycidate prepared by the method using sodium ethoxide, was undepressed.

Hofmann Reaction of 3-(p-Chlorophenyl)glycidamide:

Dry finely powdered 3-(p-chlorophenyl)glycidamide (1.97 g) was added with stirring to cooled sodium hypobromite solution, prepared from bromine (0.6 cc) and sodium hydroxide (2.4 g) dissolved in water (20 cc), at 0°. After ten minutes stirring the whole mass became very thick and difficult to stir. The reaction mixture was heated to 60-65° for 45 minutes on a water bath. After 25 minutes heating, the whole mass (semi-solid) went

into solution. After ten more minutes a solid (sodium salt) precipitated out. The reaction mixture was distilled with steam. The precipitated solid went into solution on distillation. The steam distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulphate.

Ether was distilled off from a portion of the ether extract. Infra-red spectrum (fig-15) of the residue shows bands at 2250 cm^{-1} (cf. isocyanide[89,90]), 1700 cm^{-1} (cf. aromatic aldehyde[99]) and 3400 & 3500 cm^{-1} (cf. aromatic amine[100]).

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from a portion of dried ether extract of the steam distillate. To the residue 2:4-dinitrophenylhydrazine reagent was added. The precipitated 2:4-dinitrophenylhydrazone was filtered. Crystallisation from benzene-petrol gave crystals melting at 264-5°. Mixed melting point with 2:4-dinitrophenylhydrazone of p-chlorobenzaldehyde was undepressed.

(b) Non Carbonyl Component:

Ether was distilled off from another portion of the ether extract of the steam distillate. To the residue benzoyl chloride (0.5 cc) and sodium hydroxide solution (10%; 25 cc) was added and the reaction mixture was shaken for 30 minutes.

The crude benzoyl derivative was filtered, washed with sodium hydroxide solution and water. Crystallisation from benzene-petrol gave needles m.p. 193°. Mixed melting point with the benzoyl derivative of p-chloroaniline was undepressed.

Starting from 1.97 g 3-(p-chlorophenyl)glycidamide, 45 mg of benzoyl derivative of p-chloroaniline and 35 mg of 2:4-dinitrophenylhydrazone of p-chlorobenzaldehyde were obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and the ether was distilled off. No residue was obtained.

(b) Acid Component:

The aqueous layer left after extraction of non acid component was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate. Removal of ether by distillation gave a brown coloured residue (1.6 g). Repeated crystallisation of the residue from benzene-petrol gave an acid m.p. 240°(0.5 g). Mixed melting point with p-chlorobenzoic acid was undepressed. The aqueous layer left after extraction of the acid component

was subjected to continuous ether extraction for 40 hours. Ether extract was dried over anhydrous sodium sulphate and ether was distilled off. Repeated crystallisation of the residue from benzene-methanol gave an acid m.p. 121-23° (60 mg). The acid was soluble in water and showed negative test for nitrogen. A pinch of the acid was warmed with conc. sulphuric acid and to the cooled solution two drops of 5% alcoholic guaiacol solution was added. A red violet colour was obtained (cf. test for hydroxy acids[93]). Mixed melting point with the hydroxy acid obtained by the alkaline hydrolysis of ethyl 3-(p-chlorophenyl)glycidate showed no depression.

Alkaline Hydrolysis of Ethyl 3-(p-chlorophenyl)glycidate:

Ethyl 3-(p-chlorophenyl)glycidate was hydrolysed in a manner similar to that described for the hydrolysis of ethyl 3-(m-chlorophenyl)glycidate. From 1 g ethyl 3-(p-chlorophenyl)glycidate 0.6 g of an acid m.p. 122-4° was obtained. The acid showed positive colour test of hydroxy acids with guaiacol and conc. sulphuric acid.

Analysis:

	C	H	Cl
Cal. for $C_9H_9O_4Cl$	49.70	4.16	16.38
Found	49.85	3.14	16.6

Hofmann Reaction of 3-(p-Toluyl)glycidamide

Preparation of Ethyl 3-(p-toluyl)glycidate:

Ethyl 3-(p-toluyl)glycidate was prepared by condensing p-tolualdehyde (30 g) and ethyl chloroacetate (30.6 g) in the presence of sodium ethoxide (18.7 g) in dry benzene (150 cc) as solvent. Details of the procedure were the same as described for the preparation of ethyl 3-phenylglycidate. Distillation gave ethyl 3-(p-toluyl)glycidate b.p. 150°/3 mm (reported[63,67] 119-23°/0.5 mm & 155-60°/3-4 mm) Yield 21 g.

The ester did not give any colour with alcoholic ferric chloride solution and gave negative beilsteins test for halogens.

Preparation 3-(p-Toluyl)glycidamide:

Ethyl 3-(p-toluyl)glycidate (20 g) was dissolved in alcohol (200 cc) and to the solution liquor ammonia was added (100 cc). Ammonia gas was passed in the solution for two hours and the reaction mixture was left for two hours. Alcohol was removed under suction and the precipitated amide was filtered. Crystallisation from methanol gave needles m.p. 180-1°. Yield 10 g.

Analysis:

	C	H	N
Cal. for $C_{10}H_{11}NO_2$	67.78	6.24	7.91
Found	67.99	6.25	8.03

Hofmann Reaction of 3-(p-Toluyl)glycidamide:

Dry finely powdered 3-(p-toluyl)glycidamide (2.66 g) was added with stirring to cooled sodium hypobromite solution prepared from bromine (0.9 cc) and sodium hydroxide (3.6 g) dissolved in water (30 cc) at 0°. On stirring for ten minutes, the whole mass became semi-solid and further stirring could not be done. The reaction mixture was heated to 60-65° for 45 minutes on a water bath. After ten minutes heating, the whole mass went into solution and a yellowish brown solution was obtained. After twenty five minutes, the clear solution became turbid and smell of isocyanide was detected along with the smell of ammonia. The reaction mixture was distilled with steam. The steam distillate had the smell of isocyanide. The steam distillate was extracted with ether. The ether extract was dried over anhydrous sodium sulphate.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from a portion of ether extract. 2:4-dinitrophenylhydrazine reagent was added to the

residue. Filtration and crystallisation of the 2:4-dinitrophenylhydrazone gave crystals m.p. 233-4° (benzene-petrol). Mixed melting point with 2:4-dinitrophenylhydrazone of p-tolualdehyde showed no depression. The infra-red spectrum of the 2:4-dinitrophenylhydrazone was also identical with infra-red spectrum of 2:4-dinitrophenylhydrazone of p-tolualdehyde.

(b) Non Carbonyl Component:

Ether was distilled off from the other portion of the ether extract of the steam distillate. To the residue benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution (25 cc) were added and the reaction mixture was shaken for 30 minutes. The benzoyl derivative was filtered, washed with sodium hydroxide solution and water. Crystallisation from benzene-petrol gave needles m.p. 156-7°. Mixed melting point with benzoyl derivative of p-toludine showed no depression. The infra-red spectrum of the benzoyl derivative was also identical with the infra-red spectrum of the benzoyl derivative of p-toludine.

Starting from 2.65 g of 3-(p-toluyl)glycidamide 20 mg of 2:4-dinitrophenylhydrazone of p-tolualdehyde and 20 mg of benzoyl derivative of p-toludine were obtained.

(c) Water Soluble Component:

The aqueous layer left after ether extraction of

steam distillate gave no 2:4-dinitrophenylhydrazone on treatment with 2:4-dinitrophenylhydrazine reagent.

Non Steam Volatile Portion

(a) Non Acid Portion:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. No residue was obtained.

(b) Acid Portion:

The aqueous layer left after ether extraction of the non acid portion was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. A gummy residue (1.3g) was obtained. Repeated crystallisation of the residue from benzene-petrol gave an acid m.p. 178°. (0.4 g). Mixed melting point with p-toluic acid was not depressed. The rest of the mass could not be crystallised. The aqueous layer left after extraction of acid component was subjected to continuous ether extraction for 40 hours. Ether extract was dried and ether was distilled off. Crystallisation of the residue from benzene-methanol gave an acid m.p. 123-5°. The acid was soluble in water and gave negative test for nitrogen. It gave red-violet colour on

warming with conc. sulphuric acid and adding two drops of 5% alcoholic guaiacol solution. About 20 mg of the hydroxy acid was obtained.

Analysis:

	C	H
Cal. for $C_{10}H_{12}O_4$	61.21	6.17
Found	61.56	6.44

Hofmann Reaction of 2-Methyl-3-phenylglycidamide

Preparation of Ethyl 2-methyl-3-phenylglycidate:

Ethyl 2-methyl-3-phenylglycidate was prepared by the condensation of ethyl α-bromopropionate (45.3 g) and benzaldehyde (26.5 g) in the presence of sodium ethoxide (18.7 g) as condensing agent and dry ether (300 cc) as solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)-glycidate. Distillation gave ethyl 2-methyl-3-phenyl-glycidate b.p. 110-12°/1 mm (reported[104] 117-21°/4 mm). Yield 24 g.

The glycidic ester did not give any colour with ferric chloride solution and gave negative beilstein's test for halogens.

Preparation of 2-Methyl-3-phenylglycidamide:

Ethyl-2-methyl-3-phenylglycidate (12 g) was dissolved in alcohol (120 cc) and to the solution liquor ammonia (60 cc) was added. Ammonia gas was passed in the solution for two hours and the reaction mixture was left for four hours. Alcohol was removed under suction and the precipitated amide was filtered. Crystallisation gave needles m.p. 134°(methanol) (reported[56] 134°). Yield 4.3 g.

Hofmann Reaction of 2-Methyl-3-phenylglycidamide:

Dry finely powdered 2-methyl-3-phenylglycidamide (1.77 g) was added with stirring to a solution of sodium hypobromite, prepared from bromine (0.6 cc) and sodium hydroxide (2.4 g) dissolved in water (20 cc), at 0°. The amide dissolved in the hypobromite solution after 20 minutes stirring. The reaction mixture was heated on a water bath to 60-65° for 45 minutes. After twenty minutes heating, the clear solution became dark and turbid followed by separation of a solid. The reaction mixture had the smell of isocyanide. The reaction mixture was distilled with steam. The steam distillate had the smell of isocyanide. The steam distillate was extracted with ether.

Infra-red spectrum of the residue obtained from ether extract of the steam distillate, shows absorption at 2225 cm^{-1}. Other bands were not very sharp.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from another portion of the ether extract of steam distillate. 2:4-dinitrophenylhydrazine reagent was added to the residue. The precipitated 2:4-dinitrophenylhydrazone was filtered. Crystallisation gave crystals m.p. 237° (benzene-petrol). Mixed melting point with 2:4-dinitrophenylhydrazone of benzaldehyde was undepressed.

(b) Non Carbonyl Component:

Ether was distilled off from another portion of the dried ether extract of the steam distillate. To the residue benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution (25 cc) were added and the reaction mixture was shaken for 20 minutes. The benzoyl derivative was filtered and was washed with sodium hydroxide solution and water. Crystallisation from benzene-petrol gave needles m.p. 162°. Mixed melting point with benzanilide was undepressed.

Starting from 1.77 g 2-methyl-3-phenylglycidamide 65 mg of 2:4-dinitrophenylhydrazone of benzaldehyde and 40 mg of benzoyl derivative of aniline were obtained.

(c) Water Soluble Component:

The aqueous layer left after ether extraction of the steam distillate was acidified and 2:4-dinitrophenyl-hydrazine reagent was added. No 2:4-dinitrophenylhydrazone was obtained.

Non Steam Volatile Portion

(a) Non Acid Portion:

The residue left after steam distillation was extracted with ether. Ether extract was dried over anhydrous sodium sulphate. Distillation of the ether from the ether extract gave no residue.

(b) Acid Component:

The aqueous layer left after ether extraction of non acid component was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. A gummy residue (13g) was obtained. The residue was extracted repeatedly with warm petrol. Evaporation of petrol and crystallisation of the residue from hot water gave an acid m.p. 121° (0.2 g). Mixed melting point with benzoic acid was undepressed. The rest of the mass could not be crystallised. About 0.15 g of the gummy mass was dissolved in minimum quantity of alcohol and 2:4-dinitrophenylhydrazine reagent was added to it. No 2:4-dinitrophenylhydrazone was obtained. Another portion of the gummy mass was warmed with iodine and sodium hydroxide solution. Iodoform was not obtained.

Hofmann Reaction of 2-Methyl-3-(p-chlorophenyl)glycidamide

Preparation of Ethyl 2-methyl-3-(p-chlorophenyl)glycidate:

p-Chlorobenzaldehyde (35.1 g) and ethyl α-bromopropionate (45.3 g) were condensed together in the presence of sodium ethoxide (18.7 g) in dry ether (300 cc) as the solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)-glycidate. Distillation gave ethyl 2-methyl-3-(p-chlorophenyl)-glycidate b.p. 143-4°/ 1 mm; n_D^{30} 1.5146; d_{20} 1.192 (The ester is reported in a patent[105]). Yield 30 g.

Infra-red spectrum of the ester (fig-4) in chloroform shows a single band at 1750 cm^{-1}. The glycidic ester did not give any colour with alcoholic ferric chloride.

Preparation of 2-Methyl-3-(p-chlorophenyl)glycidamide:

Ethyl 2-methyl-3-(p-chlorophenyl)glycidate (20 g) was dissolved in alcohol (200 cc) and liquor ammonia (100 cc) was added to it. Gaseous ammonia was passed in the solution for two hours and the reaction mixture was left for six hours. Alcohol was removed under suction and the precipitated amide separated by filtration. Crystallisation from methanol gave needles m.p. 170°. Yield 5 g.

Analysis:

	C	H	N	Cl
Cal. for $C_{10}H_{10}O_2NCl$	56.73	4.72	6.62	16.7
Found	56.84	4.80	6.19	16.9

Hofmann Reaction of 2-Methyl-3-(p-chlorophenyl)glycidamide:

Dry finely powdered 2-methyl-3-(p-chlorophenyl)-glycidamide (2.1 g) was added with stirring to a solution of sodium hypobromite, prepared from bromine (0.6 cc) and sodium hydroxide (2.4 g) dissolved in water (20 cc), at 0°. The glycidamide went into solution after 10 minutes stirring. The reaction mixture was heated to 60-65° for 45 minutes on a water bath. After fifteen minutes, turbidity appeared followed by separation of a solid (which went into solution during steam distillation). The reaction mixture was distilled with steam. The steam distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulphate. It was divided in two portions.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from one portion of the ether extract of the steam distillate. 2:4-dinitrophenyl-hydrazine reagent was added to the residue. Crystallisation of the impure 2:4-dinitrophenylhydrazone that was obtained,

gave crystals m.p. 265° (benzene-petrol). Mixed melting point with 2:4-dinitrophenylhydrazone of p-chlorobenzaldehyde was not depressed. 15 mg 2:4-dinitrophenylhydrazone was obtained.

(b) Non Carbonyl Component:

Ether was distilled off from the second portion of the ether extract of the steam distillate. To the residue benzoyl chloride (0.5 cc) and sodium hydroxide solution (10%; 25 cc) was added and the reaction mixture was shaken for 25 minutes. Crystallisation of the benzoyl derivative that was obtained gave needles m.p.193° (benzene). Mixed melting point with benzoyl derivative of p-chloroaniline was undepressed. 20 mg of benzoyl derivative of p-chloroaniline was obtained.

(c) Water Soluble Component:

The aqueous layer left after extraction of the steam distillate was acidified and 2:4-dinitrophenylhydrazine reagent was added to it. 2:4-Dinitrophenylhydrazone was not obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate. Ether was distilled off from the ether extract. No residue was obtained.

(b) Acid Portion:

The aqueous layer left after ether extraction of non acid component was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate. Removal of the ether by distillation gave a dark coloured residue (1.65 g). Crystallisation of the residue from benzene-petrol gave an acid m.p. 240° (0.5 g). Mixed melting point with p-chlorobenzoic acid was undepressed. The rest of the mass could not be separated into other fractions. About 0.15 g of the residue left after separation of p-chlorobenzoic acid was dissolved in minimum quantity of alcohol and 2:4-dinitrophenylhydrazine reagent was added to it. 2:4-Dinitrophenylhydrazone was not obtained. Another portion of the residue was warmed with iodine and sodium hydroxide solution. Iodoform was not obtained.

Hofmann Reaction of 3-(m-Nitrophenyl)glycidamide

Preparation of Ethyl 3-(m-nitrophenyl)glycidate:

Ethyl 3-(m-nitrophenyl)glycidate was prepared in a manner similar to that described for the preparation of ethyl 3-(o-chlorophenyl)glycidate. m-Nitrobenzaldehyde (37.7 g) and ethyl chloroacetate (30.6 g) were condensed together in presence of sodium ethoxide (18.7 g) in dry ether (300 cc) as solvent. The ester was extracted with ether and dried over anhydrous calcium chloride overnight. The residue obtained on removal of ether by distillation, solidified on cooling. Therefore, the crude ester was not distilled but purified by crystallisation from benzene-petrol. Crystals m.p. 54-55° were obtained. (Reported [64,88] 55.5 & 58°) Yield 16.5 g.

Preparation of 3-(m-Nitrophenyl)glycidamide:

Ethyl 3-(m-nitrophenyl)glycidate (15 g) was dissolved in alcohol (150 cc) and to the solution liquor ammonia (75 cc) was added. Gaseous ammonia was passed in the solution for half an hour and the reaction mixture was kept for one hour. Alcohol was removed under suction and the crude amide was filtered. Crystallisation from methanol gave needles m.p. 163-4° (reported[64] 180-1°). Yield 7.1 g.

Analysis:

		C	H	N
Cal. for $C_9H_8N_2O_4$		51.91	3.84	13.46
Found	(i)	51.80	3.99	12.99
	(ii)	52.04	4.07	12.89

Hofmann Reaction of 3-(m-Nitrophenyl)glycidamide:

Dry finely powdered 3-(m-nitrophenyl)glycidamide (2.08 g) was added to sodium hypobromite solution, prepared from sodium hydroxide (2.4 g) dissolved in water (20 cc) and bromine (0.6 cc), at 0°. The amide went into solution on stirring for 15 minutes. The reaction mixture was heated on a water bath to 60-65° for 45 minutes. After ten minutes heating, slight turbidity appeared which disappeared on further heating when a deep yellow coloured solution was obtained. Only smell of ammonia was detected in the reaction mixture. There was no smell of isocyanide. The reaction mixture was distilled with steam. The steam distillate was clear (not turbid) and coloured very light yellow. The steam distillate was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and divided in two portions.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from one portion of the

ether extract of the steam distillate. To the residue 2:4-dinitrophenylhydrazine reagent was added. The 2:4-dinitrophenylhydrazone that was obtained was not enough for crystallisation and identification.

(b) Non Carbonyl Component:

Ether was distilled off from the other portion of the ether extract of the steam distillate. To the residue benzoyl chloride (0.5 cc) and 10% sodium hydroxide (25 cc) were added and the reaction mixture was shaken for twenty minutes. No benzoyl derivative was obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether distilled off. A yellowish solid was obtained (50 mg). The solid showed positive test for nitrogen. To the solid benzoyl chloride (0.5 cc) and sodium hydroxide solution (25 cc of 10% solution) were added and the reaction mixture was shaken for twenty minutes. The precipitated benzoyl derivative was filtered, washed with sodium hydroxide solution and water. Crystallisation from benzene-petrol gave needles m.p. 154-5°. Mixed melting point

with benzoyl derivative of m-nitroaniline was undepressed.

Analysis:

	C	H	N
Cal. for $C_{13}H_{10}N_2O_3$	64.46	4.16	11.57
Found	64.98	4.32	11.34

(b) Acid Component:

The residue left after extraction of non acid component was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. A very dark coloured gummy residue (1.5 g) was obtained which could not be crystallised.

Hofmann Reaction of 3-(p-Methoxyphenyl)glycidamide

Preparation of Ethyl 3-(p-methoxyphenyl)glycidate:

Anisaldehyde (34 g) and ethyl chloroacetate (30.6 g) were condensed together in the presence of sodium ethoxide (18.7 g) and dry ether (300 cc) as solvent. Details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)glycidate. Distillation gave ethyl 3-(p-methoxyphenyl)glycidate b.p. 167-8°/1 mm (reported[63] 157-8°/0.5 mm). Yield 33 g. Knorr & Laage[67] reported this glycidic ester to be unstable.

Preparation of 3-(p-Methoxyphenyl)glycidamide:

Ethyl 3-(p-methoxyphenyl)glycidate (20 g) was dissolved in alcohol (200 cc) and to the solution liquor ammonia (100 cc) was added. Ammonia gas was passed in the solution for one hour and the reaction mixture was left for two hours. Alcohol was removed under suction and the amide was filtered. Crystallisation from benzene-petrol gave plates m.p. 151-2° (reported[63] 152°). The white amide turned brownish yellow on keeping for long period.

Hofmann Reaction of 3-(p-Methoxyphenyl)glycidamide:

Powdered dry 3-(p-methoxyphenyl)glycidamide (1.93 g)

was added with stirring to a solution of sodium hypobromite, prepared from bromine (0.6cc) and sodium hydroxide (2.4 g) in water (20 cc), at 0°. The amide formed a semi solid mass difficult to stir. The reaction mixture was heated to 60-65° for 45 minutes on a water bath. After ten minutes, the semi solid mass went into solution and on further heating a solid separated which again went into solution during steam distillation. The reaction mixture was distilled with steam. The steam distillate was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and it was divided in two portions.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from one portion of the ether extract of the steam distillate. To the residue 2:4-dinitrophenylhydrazine reagent was added. Crystallisation of the 2:4-dinitrophenylhydrazone that was obtained gave crystals m.p. 253-4° (benzene-petrol; 15 mg). Mixed melting point with 2:4-dinitrophenylhydrazone of anisaldehyde was not depressed.

(b) Non Carbonyl Component:

Ether was distilled off from the other portion of the ether extract of the steam distillate. There was no residue.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. To the residue (about two drops of dark coloured liquid) benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution were added and the reaction mixture was shaken for 45 minutes. Benzoyl derivative was not obtained.

(b) Acid Component:

The aqueous layer left after ether extraction of the non acid component was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulpahte and ether was distilled off. A dark gummy mass (1.4 g) was obtained. Repeated crystallisation from benzene-petrol gave an acid m.p. 184° (120 mg). Mixed melting point with with anisic acid was undepressed.

Hofmann Reaction of 3-Methyl-3-phenylglycidamide

Preparation of Ethyl 3-methyl-3-phenylglycidate:

Acetophenone (30 g) and ethyl chloroacetate (30.6 g) were condensed together in the presence of sodium ethoxide (18.7 g) as the condensing agent and dry ether (300 cc) as solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)-glycidate. Distillation gave ethyl 3-methyl-3-phenylglycidate b.p. 110°/1 mm (reported [69,106] 92-99/0.5 mm & 113-4°/3 mm). Yield 20 g.

The infra-red spectrum (fig-11) shows two bands in the 1700-1800 cm^{-1} region characterstic of glycidic esters.

Preparation of 3-Methyl-3-phenylglycidamide:

Ethyl 3-methyl-3-phenylglycidate (15 g) was dissolved in alcohol (150 cc) and liquor ammonia (75 cc) was added to it. Ammonia gas was passed in the reaction mixture for 2 hours and it was left for 3 days. Amide formation did not take place at the end of first two days. Alcohol was removed under suction. Crystallisation of the precipitated amide from methanol gave plates m.p. 167-8° (reported[3] 157-8°). Yield 5 g.

Analysis:

	C	H	N
Cal. for $C_{10}H_{11}NO_2$	67.78	6.26	7.91
Found	67.87	6.39	7.96

Hofmann Reaction of 3-Methyl-3-phenylglycidamide:

Finely powdered dry 3-methyl-3-phenylglycidamide (1.77 g) was added with stirring to a solution of sodium hypobromite, prepared from bromine (0.6 cc) and sodium hydroxide in water (20 cc), at 0°. On stirring for 15 minutes clear solution was not obtained neither the amide formed a semi-solid mass as in other cases. The reaction mixture was heated to 60-65° on a water bath for 45 minutes. The reaction mixture did not have the smell of isocyanide. The reaction mixture was distilled with steam. The steam distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulphate. The ether extract was divided in two portions.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was distilled off from one portion of the ether extract of steam distillate. 2:4-dinitrophenylhydrazine reagent was added to the residue. Crystallisation of the 2:4-dinitrophenylhydrazone, that was obtained, gave orange crystals m.p. 250° (benzene-petrol; 15 mg). Mixed melting point with 2:4-dinitrophenylhydrazone of acetophenone was not depressed.

(b) Non Carbonyl Component:

Ether was distilled off from the other portion of the ether extract of steam distillate. No residue was obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulpahte and the ether was distilled off. The residue solidified on cooling. Crystallisation gave a solid m.p. 168° (methanol) (50 mg). Mixed melting point with 3-methyl-3-phenylglycidamide was undepressed.

(b) Acid Component:

The aqueous layer left after extraction of the non acid component was acidified and extracted with ether. The ether extract was dried over anhydrous sodium sulphate. Distillation of the ether from the ether extract gave a dark syrupy liquid (0.85 g). The syrupy mass could not be crys-tallised.

Hofmann Reaction of 3,3-Diphenylglycidamide

Preparation of Ethyl 3,3-diphenylglycidate:

Benzophenone (45,5 g) and ethyl chloroacetate (30.6 g) were condensed together in the presence of sodium ethoxide (18.7 g) and dry ether (350 cc) which was used as solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)glycidate. Distillation gave ethyl 3,3-diphenylglycidate b.p. 165-75°/2-3 mm (reported[65] 152-3°/1 mm; solidifies immediately after distillation). Yield 40 g. The ester did not solidify immediately after distillation. However, crystals appeared after three days and the whole mass solidified after a week.

Preparation of 3,3-Diphenylglycidamide:

Ethyl 3,3-diphenylglycidate (20 g) was dissolved in alcohol (200 cc) and to the solution liquor ammonia (100 cc) was added. Ammonia gas was passed in the solution for two hours and the reaction mixture was left for four days. Alcohol was removed under suction and the precipitated amide filtered out. Crystallisation from methanol gave needles m.p. 148° (reported[3,65] 126-7° & 148°). Yield 8.5 g.

Hofmann Reaction of 3,3-Diphenylglycidamide:

3,3-Diphenylglycidamide (2.4 g) was added with

stirring to a solution of sodium hypobromite, prepared from bromine (0.6 cc) and sodium hydroxide (2.4 g) dissolved in water (20 cc), at 0^{o}. The glycidamide was not soluble in the hypobromite solution nor it formed a semi solid mass as was observed in other cases. The reaction mixture was heated on a water bath to 60-65^{o} for 45 minutes. On heating the amide went into solution and after about twenty minutes, turbidity appeared followed by precipitation of an oily solid which settled in the bottom of the flask. At this stage, a clear but faint smell of isocyanide along with smell of ammonia was detected. The reaction mixture was distilled with steam. The steam distillate was turbid and it did not have the smell of isocyanide. The steam distillation was stopped when about 250 cc of the steam distillate was collected. The steam distillate was acidified with hydrochloric acid and extracted with ether. The ether extract was subsequently tested for carbonyl component. To a portion of acidified aqueous layer left after ether extraction, sodium nitrite solution was added in cold and to it alkaline β-naphthol solution was added. No dye was obtained. The rest of the aqueous layer was basified with sodium hydroxide solution and extracted with ether. The ether extract was tested for the non carbonyl component.

Steam Volatile Portion

(a) Carbonyl Component:

The ether extract was dried over anhydrous sodium sulphate and the ether was distilled off. To the residue 2:4-dinitrophenylhydrazine reagent was added. Crystallisation of the 2:4-dinitrophenylhydrazone that was obtained, from benzene-petrol(40-60°) gave orange crystals m.p. 238°. (Mixed melting point with 2:4-dinitrophenylhydrazone of benzophenone was not depressed.

(b) Non Carbonyl Component:

The ether extract was dried over anhydrous sodium sulphate and ether was distilled off. No residue was obtained.

Non Steam Volatile Portion

The oily solid which remained in the distilling flask after steam distillation was filtered. It was found to be insoluble in ether, alcohol, benzene, petroleum ether 40-60 & 60-80°, ethyl acetate and chloroform. It was very slightly soluble in benzene and alcohol. The solid was heated with excess of benzene and filtered. The filtrate on concentration gave a partially purified product m.p. 240-50°.

The filtrate left after separation of the solid was extracted with ether before and after acidification and dried over anhydrous sodium sulphate. Ether was distilled off. No residue was obtained in both the cases.

Hofmann Reaction of 2,3-Diphenylglycidamide

Preparation of Ethyl 2,3-diphenylglycidate

Benzaldehyde (17.6 g; 0.167 mole) and ethyl α-chlorophenylacetate (33.1 g; 0.167 mole) (prepared by the method described by Zimmerman[73] from mandelic acid and phosphorus pentachloride) were condensed together in the presence of sodium ethoxide (12.7 g) in 150 cc dry ether as solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)-glycidate. After the reaction the glycidic ester was extracted with ether. The ether extract was dried over anhydrous sodium sulphate. Removal of ether by distillation gave a residue which solidified on cooling. Crystallisation of the residue from methanol gave needles m.p. 59-60°(reported[73,104] 57-8° & 59-60°). Yield 25 g.

Preparation of 2,3-Diphenylglycidamide:

Gaseous ammonia was passed into a solution of ethyl 2,3-diphenylglycidate (15 g) in alcohol (150 cc) to which liquor ammonia (75 cc) was already added, for one hour. The reaction mixture was kept for two hours. Alcohol was removed under suction and the precipitated amide separated by filtration. Crystallisation from benzene-petrol(40-60°) gave needles m.p. 133-34°.(Reported[53] cis amide 133-4 and trans

amide 202-3°) Yield 8.3 g.

Analysis:

	C	H	N
Cal. for $C_{15}H_{13}NO_2$	75.30	5.48	5.85
Found	75.88	5.65	5.72

Hofmann Reaction of 2,3-Diphenylglycidamide

Finely divided dry 2,3-diphenylglycidamide (2.4) was added with stirring to sodium hypobromite solution prepared from sodium hydroxide (2.4 g) dissolved in water (20 cc) and bromine (0.6 cc) at 0°. The reaction mixture was stirred for 30 minutes but amide did not dissolve in the hypobromite solution nor it formed a semi-solid mass. The reaction mixture was heated to 60-65° for 45 minutes on a water bath. After heating for twenty five minutes an oily layer separated but smell of isocyanide was not detected. The reaction mixture was distilled with steam. The steam distillate was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and the dried extract was divided in two portions.

Steam Volatile Portion

(a) Carbonyl Component:

Ether was removed by distillation from one portion of the ether extract. 2;4-dinitrophenylhydrazine reagent was added

to the residue. Crystallisation of the 2:4-dinitrophenyl-hydrazone gave crystals m.p. 237° (20 mg). Mixed melting point with 2:4-dinitrophenylhydrazone of benzaldehyde was not depressed.

(b) Non Carbonyl Component:

Ether was distilled off from other portion of the dried ether extract. No residue was obtained.

Non Steam Volatile Portion

(a) Non Acid Component:

The aqueous layer left after steam distillation was extracted with ether and dried over anhydrous sodium sulphate. Ether was distilled off. About 4-5 drops of very dark coloured residue was obtained. Benzoyl chloride (0.5 cc) and 10% sodium hydroxide solution (25 cc) were added to it and the reaction mixture was shaken for 30 minutes. No benzoyl derivative was obtained.

(b) Acid Component:

The aqueous layer left after extraction of non acid component was acidified with hydrochloric acid and extracted with ether. Ether was distilled off after drying over anhydrous sodium sulphate. A gummy mass (1.8 g) was obtained. Repeated

extraction with petrol (40-60) gave an acid m.p. 121° (50 mg) (water). Mixed melting point with benzoic acid was not depressed. The rest of the mass could not be crystallised into other fractions.

Hofmann Reaction of 3,3-Pentamethyleneglycidamide

Preparation of Ethyl 3,3-pentamethyleneglycidate:

Cyclohexanone (24.5 g) and ethyl chloroacetate (30.6 g) were condensed together in the presence of sodium ethoxide (18.7 g) as condensing agent and dry ether (300 cc) as solvent. The details of the procedure were the same as described for the preparation of ethyl 3-(o-chlorophenyl)glycidate. Distillation gave ethyl 3,3-pentamethyleneglycidate b.p. 100°/1 mm (reported[107] 81-3°/.04 mm & 115-7°/10 mm) Yield 29 g.

Preparation of 3,3-Pentamethyleneglycidamide:

Ethyl 3,3-pentamethyleneglycidate (25 g) was dissolved in alcohol (250 cc) and to the solution liquor ammonia (125 cc) was added. Ammonia gas was passed in the solution for 3 hours. The reaction mixture was left for three days.(Amide formation did not take place after two days.) Alcohol was removed under suction and the precipitated amide was filtered. Crystallisation from methanol gave needles m.p. 138-9° (reported[3] 139°). Yield 12 g.

Hofmann Reaction of 3,3-pentamethyleneglycidamide:

Dry finely powdered 3,3-pentamethyleneglycidamide was added with stirring to sodium hypobromite solution, prepared

from bromine (0.6 cc) and sodium hydroxide (2.4 g) dissolved in water (20 cc), at 0°. The glycidamide went into solution after twenty minutes stirring. The reaction mixture was heated to 60-65° for 45 minutes on a water bath. There was no smell of isocyanide. The reaction mixture was distilled with steam. The steam distillate was acidified with hydrochloric acid and extracted with ether. The ether extract was tested for carbonyl component. The aqueous layer was made alkaline with sodium hydroxide solution and extracted again with ether. The ether extract was tested for non carbonyl component (for amine).

Steam Volatile Portion

(a) Carbonyl Component:

The ether extract was dried and ether distilled off. 2:4-dinitrophenylhydrazine reagent was added to the residue. Crystallisation of the 2:4-dinitrophenylhydrazone that was formed, from benzene-petrol (40-60°) gave crystals m.p. 159-160° (15 mg). Mixed melting point with 2:4-dinitrophenylhydrazone of cyclohexanone showed no depression.

(b) Non Carbonyl Component:

The ether extract was dried over anhydrous sodium sulphate. Distillation of ether left no residue.

Non Steam Volatile Portion

(a) Non Acid Component:

The residue left after steam distillation was extracted with ether. The ether extract was dried over anhydrous sodium sulphate and the ether was distilled off. No residue was obtained.

(b) Acid Component:

The aqueous layer left after extraction of non acid component was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and ether was removed by distillation. A dark coloured gummy residue (1 g) was obtained. The gummy residue could not be crystallised.

Preparation of Ethyl 3-(α-furyl)glycidate:

Furfural (20 g; 0.25 mole) and ethyl chloroacetate (30.6 g; 0.25 mole) were condensed together in the presence of sodium ethoxide (18.7 g; 0.275 mole) in dry benzene (150 cc) as solvent. The details of the procedure were the same as described for the preparation of 3-phenylglycidic ester. After the reaction the glycidic ester was extracted with ether. The ether extract was dried over anhydrous sodium sulphate. Ether was distilled off and the residue was transfered to a flask with a built in condenser and a coleumn. However, during distillation under reduced pressure, the glycidic ester turned black and lot of fumes were evolved (The ester decomposed).

C O N C L U S I O N S

C O N C L U S I O N S

1. Hofmann reaction under normal conditions using aqueous alakline sodium hypobromite was studied on 3-phenylglycidamide, 3-(o-chlorophenyl)glycidamide, 3-(m-chlorophenyl)glycidamide, 3-(p-toluyl)glycidamide, 3-(p-chlorophenyl)glycidamide, 3-(m-nitrophenyl)-glycidamide, 3-(p-methoxyphenyl)glycidamide, 2-methyl-3-phenylglycidamide, 2-methyl-3-(p-chlorophenyl)-glycidamide, 2,3-diphenylglycidamide, 3,3-diphenyl-glycidamide, 3-methyl-3-phenylglycidamide and 3,3-pentamethyleneglycidamide. Glycidamines, the normal reaction product of the Hofmann reaction or the hydroxy aldehydes, into which the glycidamines may decompose, were not obtained in any of the examples studied.

2. Hofmann reaction of 3-phenylglycidamide, under special conditions using methanolic sodium methoxide and bromine, did not give the expected urethane.

3. On the basis of reaction products obtained in the Hofmann reaction of glycidamides it is concluded that the reaction of alkaline sodium hypobromite on glycidamides proceeds along three different paths simultaneously i.e. (a) oxidation resulting in the formation of aldehydes and carboxylic acids (b) hydrolysis resulting in the formation of glyceric acids and (c) an abnormal Hofmann reaction resulting in the formation of isocyanides and amines.

TABULAR SURVEY OF HOFMANN REACTION FROM 1942 TO 1964

S.No.	Amide	Reagent	Product	R
1.	1-D-Xylopyranosidoglyoxaline-4:5-dicarboxyamide	KOBr	9-D-Xylopyranosidoxanthine	
2.	1-D-Mannopyranosidoglyoxaline-4:5-dicarboxyamide	"	9-D-Mannopyranosidoxanthine	
3.	1-D-Ribopyranosidoglyoxaline-4:5-dicarboxyamide	"	9-D-Ribopyranosidoxanthine	
4.	1-D-Ribofuranosidoglyoxaline-4:5-dicarboxyamide	"	9-D-Ribofuranosidoxanthine	
5.	Quinolinamide	"	(a) 2:6-dihydroxypyridino-(2':3'-4:5)-pyrimidine (b) 2-Aminonicotinic acid	
6.	o-Cyanobenzamide	NaOCl	2:4-Dihydroxyquinazoline	
7.	α-Iminophthalide	"	"	
8.	6-Methylcinchomeronimide-α-imine	"	2:4-Dihydroxy-6-methyl-copazoline	
9.	Quinoxaline-2:3-dicarboxyamide	KOBr (2 Mol)	Alloxazine	
10.	"	KOBr (1 Mol)	2-Aminoquinoxaline-3-carboxylic acid	
11.	Glyoxaline-4:5-dicarboxyamide	KOBr	Xanthine	
12.	1-Methylglyoxaline-4:5-dicarboxyamide	"	9-Methylxanthine	

S.No.	Amide	Reagent	Product
13.	N-Methylphthalamide	KOBr	3-Methyl-2:4-diketo-1:2:3:4-tetrahydroquinazoline
14.	N-Ethylphthalamide	"	3-Ethyl-2:4-diketo-1:2:3:4-tetrahydroquinazoline
15.	4-Nitrophthalamide	"	4- and 5-Nitroanthranilic acids
16.	3-Nitrophthalamide	"	6-Nitroanthranilic acid
17.	4-Chlorophthalamide	"	4-Chloroanthranilic acid
18.	3-Chlorophthalimide	"	3-Chloroanthranilic acid
19.	3-Bromophthalimide	"	3-Bromoanthranilic acid
20.	3-Iodophthalimide	"	3-Iodoanthranilic acid
21.	3-methyl-5-pyrazolecarboxamide	"	3-Methyl-4-bromo-5-pyrazole carboxamide
22.	3-Methyl-4-bromo-5-pyrazole-carboxamide	"	3-Methyl-4-bromo-5-amino-pyrazole
23.	3-Methyl-4-nitro-5-pyrazole-carboxamide	"	3-Methyl-4-nitro-5-amino-pyrazole
24.	5-Pyrazolecarboxamide	"	4-Bromo-5-pyrazolecarboxamide
25.	3,5-Dimethyl-1-pyrazolecarbo-xamide	"	3,5-dimethyl-4-bromopyrazole

S.No.	Amide	Reagent	Product
26.	∝-Isopropylvaleramide	Br/Alkali 1 Mole	(a) 1-Isopropylbutylamine (b) 1,3-bis(1-isopropylbutyl)-urea
27.	∝-Isoamylenanthamide	"	(a) Diisoamylmethylisocyanate (b) 1,3-bis(diisoamylmethyl)-urea
28.	∝-Isopropylvaleramide	Br/Alakli .5 Mole	(a) 1,3-bis(1-isopropylbutyl)-urea (b) Unchange amide
29.	∝-Isoamylisoenanthamide	"	(a) 1,3-bis(diisoamylmethyl)-urea (b) Unchanged amide
30.	Hexadecylmalonamic acid	Not mentioned	∝-Aminostearic acid
31.	Diphenylacetamide	KOBr	Benzhydrylamine
32.	β,β-Diphenylpropionamide	"	β,β-Diphenylethylamine
33.	Diphenylacetamide	KOBr	N-Benzhydrylbenzophenone-imine
34.	Benzilic acid amide	KOBr	Benzophenone
35.	2-Chloro-3-methylbenzamide	NaOCl	2-Chloro-3-methylaniline
36.	(+) 2-Methyl-2-phenylcaproamide	"	(+) 2-Amino-2-phenylhexane

S. No.	Amide	Reagent	Product	R
37.	Ethyl [1-(Carbamylmethyl)-heptyl]-carbamate	KOBr	(a) 3-Carbethoxy-4-hexyl-2-imidazolidone (b) 5-Hexylhydantoin (c) Unchanged amide	1
38.	1-Enanthylurea	NaOBr	(a) 5-Hexyl-1,2,3,4-oxadiazol-2(3H)one (b) Enanthic acid	1
39.	Amide of N-acylated-β-phenyl-β-alanine	Not mentioned	5-Phenyl-1,3,4-oxadiazol-2(3H)one	1
40.	Phenylglyoxalidine	NaOBr	(a) " (b) Unreacted amide (c) Unidentified products	1
41.	2-Phenylhydantoic acid	KOBr	(a) Benzaldehyde (b) Benzoic acid (c) Unreacted amide	1
42.	5-Phenylhydantoin	"	5-Phenyl-1,3,4-oxadiazol-2(3H)one	1
43.	Benzoylurea	"	(a) " (b) Benzoic acid	1
44.	γ-Ethyl-β-aminooctanamide	"	(a) 5-(1-Ethylpentyl)-1-benzoyl-2-imidazolidinone (b) 5-(1-Ethylpentyl)-2-imidazolidinone (c) Benzoic acid (d) Unidentified products	1

S.No.	Amide	Reagent	Product	R
45.	N-[α-(Carbamoylmethyl)-benzyl]-benzanilide	KOBr	N-[α-(aminomethyl)benzyl]-benzanilide	1
46.	β-Benzamido-3,4-methylenedioxyhydrocinnamide	"	(a) 5-(3,4-Methylenedioxyphenyl) glyoxalidone (b) 5-(3,4-Methylenedioxyphenyl) 1,3,4-oxadiazol-2-one	1
47.	β-Benzamido-p-methoxyhydrocinnamide	"	(a) 5-(4-methoxyphenyl)glyoxalidone (b) 5-(4-Methoxyphenyl)1,3,4-oxadiazol-2-one	1
48.	2-Bromo-2-ethylbutyramide	NaOBr	Diethylketone	
49.	2-Bromo-3-methylbutyramide	"	Isobutyraldehyde	
50.	2-Bromoheptanamide	NaOCl	Hexanal	
51.	2-Bromoundecanamide	$NaOCl/CH_3OH$	Decanal	
52.	2-Bromoundecanamide	$NaOBr/CH_3OH$	Decanal	
53.	2-Chlorohexanamide	NaOCl	Valeraldehyde	
54.	2,5-Dibromoadipamide	"	Succinic acid	
55.	2-Chloro-2-methylbutyramide	NaOBr	Ethyl methyl ketone	
56.	2-Bromo-2-methylbutyramide	"	Ethyl methyl ketone	
57.	2-Chloro-2-ethylbutyramide	"	Diethyl ketone	
58.	2-Bromo-2-ethylbutyramide	"	Diethyl ketone	

S. No.	Amide	Reagent	Product
59.	2-Chloro-2-ethylhexanamide	NaOBr	n-Butyl ethyl ketone
60.	2-Bromo-2-ethylhexanamide	"	n-Butyl ethyl ketone
61.	1-Chlorocyclohexanecarboxamide	"	Cyclohexanone
62.	1-Bromocyclohexanecarboxamide	"	Cyclohexanone
63.	β-Chloroisobutyramide	"	2-Amino-1-propanol
64.	Perfluorobutyramide	"	n-Perfluoropropylbromide
65.	Perfluorobutyramide	NaOCl	(a) n-Perfluoropropylchloride (b) Monohydroperfluoroethane (c) Perfluoropropylene
66.	Perfluorobutyramide	NaOI	Perfluoropropylhydride
67.	Perfluoroacetamide	NaOBr	Ammonia and Carbonmonoxide
68.	N-Bromoperfluorobutyramide	30% NaOH	n-Bromoperfluoropropane
69.	N-Bromoperfluoroacetamide	"	Bromotrifluoromethane
70.	N-Iodoperfluorobutyramide	"	(a) n-Hydroperfluoropropane (b) Perfluoropropylene (c) Ammonia
71.	Trichloroacetamide	KOBr	Trichloromethylamine[ii]
72.	β-Hydroxy-β-phenylpropionamide	Br_2/$NaOCH_3$ methanol	5-Phenyloxazolid-2-one

S.No.	Amide	Reagent	Product
72.	Salicylamide	NaoCl in strogly basic soln.	4:5-benzoxazol-2-one
73.	Salicylamide	NaOCl in less basic solution	3- and 5-Chloro-2-hydroxy-benzamides
74.	Chloroacetamide	Procedure B[m]	Formaldehyde, Bromochloro-methane and Glycollic acid
75.	2-Chloropropionamide	Proc. B	(a) Acetaldehyde (b) 1-Chloro-1-bromoethane (c) Lactic acid
76.	2-Chloropropionamide	Proc. A	1-Chloro-1-bromoethane
77.	2-Bromopropionamide	Proc. A	1,1-Dibromoethane
78.	2-Chlorobutyramide	Proc. B	(a) Propionaldehyde (b) 1-bromo-1-chloropropane (c) 2-Hydroxybutyric acid
79.	2-Bromobutyramide	Proc. B	(a) Propionaldehyde (b) 1,1-Dibromopropane (c) 2-Hydroxybutyric acid
80.	2-Bromopropionamide	Proc. B	(a) Acetaldehyde (b) 1,1-Dibromoethane (c) Lactic acid
81.	2-Chloroisobutyramide	Proc. B	(a) Acetone (b) 2-Bromo-2-chloropropane

S.No.	Amide	Reagent	Product	Ref.
82.	2-Chloroisobutyramide	Proc. A	(a) Acetone (b) 2-Bromo-2-chloropropane (c) 2-Hydroxyisobutyric acid	26
83.	2-Bromoisobutyramide	Proc. A	(a) Acetone (b) 2,2-Dibromopropane (c) 2-Hydroxyisobutyric acid	26
84.	2-Bromoisobutyramide	Proc. B	(a) Acetone (b) 2,2-Dibromopropane	26
85.	α-Chloromethylethylacetamide	Proc. B	(a) Methyl ethyl ketone (b) 2-Chloro-2-bromobutane (c) 2-Methyl-2-hydroxybutyric acid	26
86.	α-Chlorodiethylacetamide	Proc. B.	(a) Diethyl ketone (b) 3-Chloro-3-bromopentane (c) 2-Ethyl-2-hydroxybutyric acid	26
87.	3,4,5-Trimethoxy-α,α-dimethylhydrocinnamide	KOBr	α-α-Dimethylmescaline	117
88.	1-(p-Carbamoylphenylsulphonyl)-urea	Not Mentioned	Sulphanilylurea	118
89.	Ethyl N-bromo-α,α-diisopropylmalonamate	NaOH	α,α-Diisopropyl-α-aminoacetic acid	13
90.	Ethyl N-bromo-α,α-dipropylmalonamate	"	α,α-Dipropyl-α-aminoacetic acid	13

S.No.	Amide	Reagent	Product	Ref.
91.	Ethyl N-bromo-α,α-dibutylmalonamate	NaOH	α,α-Dibutyl-α-amino-acetic acid	13
92.	Ethyl N-bromo-α,α-diisobutylmalonamate	"	α,α-Diisobutyl-α-amino-acetic acid	13
93.	Ethyl N-bromo-α,α-diisoamylmalonamate	"	α,α-Diisoamyl-α-amino-acetic acid	13
94.	Ethyl N-bromo-α-ethyl-α-propylmalonamate	"	α-Ethyl-α-propyl-α-amino-acetic acid	13
95.	Ethyl N-bromo-α-propyl-α-isopropylmalonamate isopropylmalonamate	"	α-Amino-α-isopropylvaleric-acid	13
96.	Ethyl N-bromo-α-isopropyl-α-butylmalonamate	"	α-Amino-α-isopropylcaproic-acid	13
97.	4-Hydroxyphthalimide	Not mentioned	2-Amino-5-hydroxybenzoic acid	119
98.	Bromophthalimide	CH_3OH and $NaOCH_3$	(a) Dimethylcarboxyanthranilate (b) Dimethyl carboxycarbanilylphthalamate	28
99.	Succinic acid semiamide sodium salt	$NaOBr^{iv}$	β-Alanine ethylester	39
100.	Glutaric acid semiamide sodium salt	NaOCl	Dipyrrolidinone	39

S.No.	Amide	Reagent	Product
101.	Adipic acid semiamide methyl ester	$NaOBr^{V}$ CH_3OH	5-Aminovaleric acid
102.	Pimelic acid semiamide methyl ester	"	6-Aminohexanoic acid
103.	Suberic acid semiamide methyl ester	"	7-Aminoheptanoic acid
104.	Azelaic acid semiamide methyl ester	"	8-Aminooctanoic acid
105.	Sebacic acid semiamide methyl ester	"	9-Aminononanoic acid
106.	Tetradecanedioic acid semiamide methyl ester	"	13-Aminotridecanoic acid
107.	Nitroacetamide	NaOBr	Dibromonitromethane
108.	β-(1-Benzimidazole)-propionamide	"	1-(β-Aminoethyl)-benzimidazole
109.	β-(2-Methyl-1-benzimidazole)-propionamide	"	2-Methyl-1-(β-aminoethyl)-benzimidazole
110.	β-(2-Isopropyl-1-benzimidazole)propionamide	"	2-Isopropyl-1-(β-aminoethyl)benzimidazole
111.	β-(2-Benzyl-1-benzimi-)dazole)propionamide	"	2-Benzyl-1-(β-aminoethyl)-benzimidazole

S.No.	Amide	Reagent	Product	R
112.	α-Methyl-β (1-benzimidazole) propionamide[vi]	NaOBr	1-(β-Methyl-β-aminoethyl)-benzimidazole	
113.	Caproamide	NaOCl	Amylamine	
114.	Pelargonamide	"	Octylamine	
115.	Heptanamide	"	Hexylamine	
116.	Octanamide	"	Heptylamine	
117.	Octanamide	NaOCl[vii]	Heptylamine	
118.	Pelargonamide	"	Octylamine	
119.	Capramide	"	Nonylamine	
120.	Lauramide	"	Undecylamine	
121.	Tridecanamide	"	Dodecylamine	
122.	Lauramide	NaOCl and CH_3OH	Methyl-N-undecylcarbamate	
123.	Palmitamide	"	Methyl-N-pentadecyl-carbamate	
124.	Ethyl-2-carbamoyl-3-methylvalerate	Not mentioned	Isoleucine	1
125.	Perfluorobutyramide	NaOBr	Bromoperfluoropropane	
126,	N-Bromoperfluorobutyramide sodium derivative	Heating the aq. solution	Perfluoropropylbromide	

S.No.	Amide	Reagent	Product
127.	N-Bromoperfluorobutyramide sodium derivative (anhydrous)	Pyrolysis	Perfluoropropylisocyanate
128.	Trichloroacetamide	NaOBr	(a) Bromotrichloromethane (b) Sodium Cyanate (c) Chloroform (d) Ammonia
129.	N-Bromotrichloroacetamide	NaOH	(a) Bromotrichloromethane (b) Chloroform (c) Sodium cyanate (d) Ammonia
130.	N-Bromotribromoacetamide	"	(a) Carbon tetrabromide (b) Bromoform (c) Sod.Cyanate (d) Ammonia
131.	Levopimaramide	KOBr	Levopimaryl isocyanate
132.	3-Phenyl-2-quinoxaline carboxamide	"	2-Amino-3-phenylquinoxaline
133.	4-Amino-2,7-diphenyl-6-pteridinecarboxamide	"	4,6-Diamino-2,7-diphenyl-pteridine
134.	2,4-Diamino-7-phenyl-6-pteridinecarboxamide	"	2,4,6-Triamino-7-phenyl-pteridine
135.	4-Amino-2,6-diphenyl-7-pteridinecarboxamide	"	4,7-Diamino-2,6-diphenyl-pteridine
136.	Paraconamide	$Br_2/Ba(OH)_2$	β-Amino-γ-hydroxybutyric acid

S.No.	Amide	Reagent	Product
137.	2-Pivaloylbenzamide	NaOBr	2-Pivaloylaniline

i. Dilute alkali solution was used. Heating was not done. The reaction mixture was stirred for ten hours at 0^{o}.

ii. Shown to be incorrect by Hine and Rosscup[22].

iii. Procedure A: Reaction mixture was allowed to remain at $0-5^{o}$ for 66 hours followed by heating to 50^{o} and steam distill
Procedure B: The reaction mixture stirred for ten minutes, heated rapidly and steam distilled.(Usual procedure for Hofm reaction)

iv. The reaction mixture was acidifie d and esterified simultaneously. amine was obtained as ethyl ester of amine hydrochloride.

v. Obtained by the hydrolysis of the carbamate.

vi. Hofmann reaction was also done with benzimidazoles having substitue in the benzene ring but the exact position of substituents is not mentioned.

vii. 33% Dioxane was used as co-solvent. The amines were obtained in improved yields.

B I B L I O G R A P H Y

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CHIMIE ORGANIQUE. — *La réaction d'Hofmann sur les glycidamides.* Note (*) de MM. **Nedumparambil A. Abraham** et **Narendra Hajela**, présentée par M. Marcel Delépine.

Les glycidamides ne donnent pas les amines attendues par la réaction d'Hofmann. Elles donnent dans cette réaction des cétones ou un mélange de cétones et d'isonitriles. On postule une migration 1 : 4 pour expliquer la formation des isonitriles.

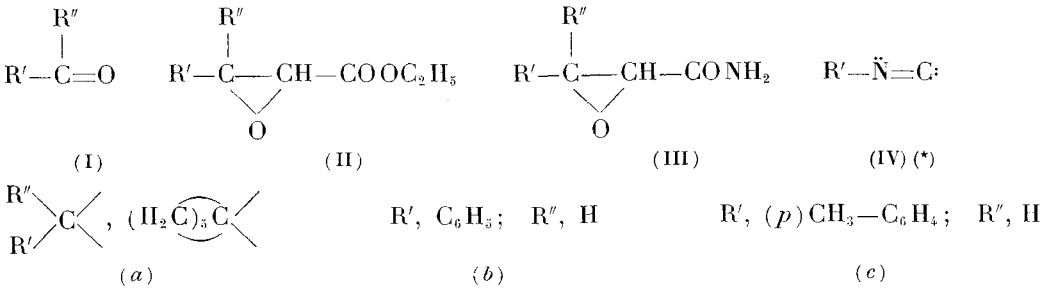
La littérature ne montre aucun exemple de la réaction d'Hofmann sur un glycidamide. Nous avons eu l'occasion de préparer quelques-uns de ces amides et d'étudier sur eux cette réaction.

Préparation des glycidamides (III) (1). — On prépare des esters glycidiques (II) par la condensation de Darzens (2) sur les composés cétoniques (I) correspondants. On laisse ces esters en contact avec l'ammoniaque en solution alcoolique. Après quelques heures et par évaporation de l'alcool les glycidamides cristallisent (III *a*, *b* et *c*).

Réaction d'Hofmann (3). — On ajoute 0,01 mole de glycidamide à une solution d'hypobromite de soude qu'on prépare à partir de 0,012 mole de brome et de 0,06 mole de soude dissous dans 20 ml d'eau. Le mélange réactionnel est chauffé pendant 30 mn à 60° sur un bain d'eau. On entraîne ensuite à la vapeur d'eau. Dans la partie entraînée, on identifie des composés cétoniques et des isonitriles.

Produits de la réaction. — A partir du β, β-pentaméthylène-glycidamide (III *a*), on n'a pu isoler comme produit de la réaction d'Hofmann que la cyclohexanone, identifiée par sa 2.4-dinitrophénylhydrazone et le spectre dans l'infrarouge. Le glycidamide III *b* donne par le même traitement deux produits : benzaldéhyde (I *b*) et isocyanure de phényle (IV *b*). On identifie le benzaldéhyde par sa 2.4-dinitrophénylhydrazone et l'isonitrile par son odeur et son spectre dans l'infrarouge ($\nu_{-C\equiv N}$: 2 225 cm^{-1}) (4).

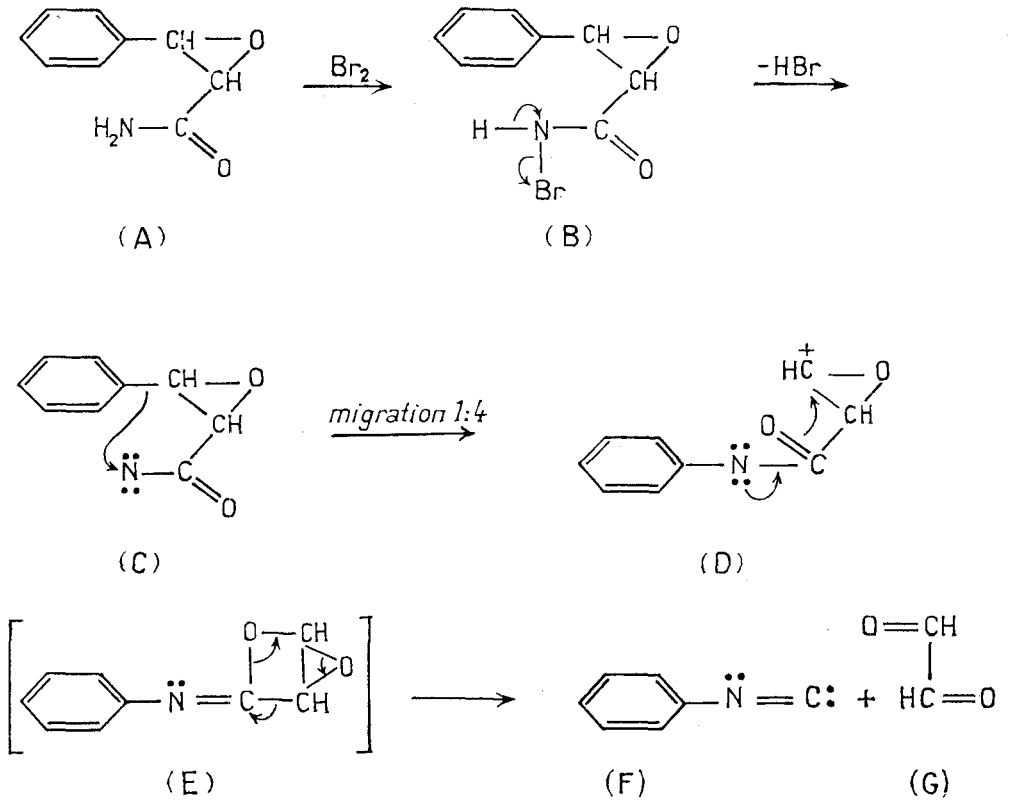
De la même façon, on identifie le *p*-toluyaldéhyde (I *c*) et l'isocyanure de *p*-toluyle (IV *c*) comme produits de la réaction d'Hofmann sur le glycidamide III *c*. Les deux isonitriles (IV *b* et IV *c*) sont convertis par l'acide chlorhydrique respectivement en aniline et *p*-toluidine, qui peuvent être diazotées ou transformées en dérivés benzoylés pour leur identification.



(*) Pour les formules (IV), le groupement R″ = H est éliminé lors de la formation d'isonitrile.

Dans le cas des glycidamides III *b* et III *c*, la partie non entraînable à la vapeur d'eau contient de l'acide glycolique, identifié par une réaction colorée ([6]) et par oxydation en acide oxalique au moyen de permanganate de potassium alcalin ([6]).

Mécanisme de la formation d'isonitrile. — C'est peut-être la première fois qu'on décrit la formation d'un isonitrile dans une réaction d'Hofmann, formation explicable par le mécanisme suivant : La réaction procède de manière classique ([5]), c'est-à-dire (A) → (B) → (C). A cette étape, une



migration 1 : 4 [au lieu de la migration 1 : 2 habituelle ([5])] du groupe phényle vers l'azote électrophile conduit au carbonium (D). Cette migration est facilitée par le voisinage du groupe phényle et de l'atome d'azote dans un « quasi » cycle à cinq atomes (C). Ce carbonium se transforme en composé bicyclique (E) qui, à cause de sa structure forcée, se décompose en isonitrile (F) et glyoxal (G). L'argument en faveur de ce mécanisme est la mise en évidence de la formation du glyoxal dans la réaction d'Hofmann sur les glycidamides III *b* et III *c*; ceci résulte de l'identification, dans la partie non entraînable à la vapeur d'eau, d'acide glycolique, lequel doit se former à partir du glyoxal par une réaction de dismutation interne.

(*) Séance du 19 novembre 1962.

(1) *Cf.* V. F. MARTYNOV et G. OLMAN, *J. Gen. Chem. U.S.S.R.*, 27, 1957, p. 1944-1952 et la suite des Mémoires.

(2) *Organic Reactions*, J. Wiley, New-York, V, 1947, p. 413.

(3) *Organic Reactions*, J. Wiley, New-York, III, 1947, p. 280.

(4) L. J. BELLAMY, *The Infra-red Spectra of Complex Molecules*, Methuen, London, 1958, p. 265.

(5) E. S. GOULD, *Mechanism and Structure in Organic Chemistry*, H. Holt, New-York, 1959, p. 621.

(6) H. MIDDLETON, *Systematic qualitative organic Analysis*, Arnold, London, 1948, p. 73.

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